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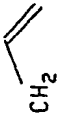
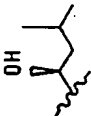
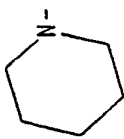
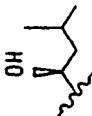
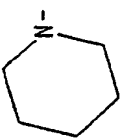
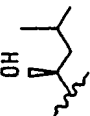
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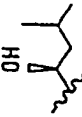
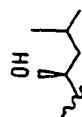
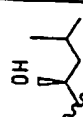
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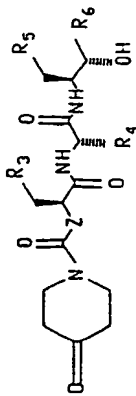
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Example	R_1, R_2, N	Z	R_3	R_4	R_5	R_6	Salt Form	FAB-MS $M^+ + H$ (%)	1H NMR (Partial)
192	Me_3N	NH	Ph				HCl	642 (100%) ^b 302 (100%)	(CDCl ₃) ^c 0.95 (d, 6H), 2.28 (s, 6H), 2.88 (dd, 1H), 3.12 (m, 1H), 3.70 (m, 1H), 4.10 (m, 1H), 4.80 (d, 1H), 5.03 (m, 2H), 5.55 (m, 1H)
193		NH	Ph	CH_2SCH_3			HCl	702 (100%) ^b 314 (20%) 413 (100%)	(CDCl ₃) ^c 0.97 (d, 6H), 2.18 (s, 3H), 2.92 (dd, 1H), 3.20 (m, 2H), 3.98 (d, 1H), 4.13 (m, 1H), 4.30 (m, 1H), 4.50 (m, 1H), 4.68 (d, 1H)
194		CH_2	Ph	CH_2SCH_3			HCl	701 (60%) ^b 154 (100%)	(CDCl ₃) ^c 0.92 (d, 1.5H), 0.93 (d, 1.5H), 0.95 (d, 3H), 2.13 (s, 1.5H), 2.14 (s, 1.5H), 3.70 (m, 1H), 4.18 (m, 1H), 4.56 (m, 1H)

Example	R ₁ R ₂ N	Z	R ₃	R ₄	R ₅	R ₆	Salt Form	FAB-MS M ⁺ +H (%)	¹ H NMR (Partial)
195	Me ₂ N-	CH ₂		CH ₂ SCH ₃	Cy*		HCl	667 (75%) ^b 307 (100%)	(CDCl ₃) ^c 0.92 (d, 3H), 0.94 (d, 3H), 2.12 (s, 3H), 2.32 (s, 6H), 2.80 (m, 1H), 2.95 (dd, 1H), 3.78 (m, 1H), 6.88 (d, 1H), 7.21 (d, 1H)
196	Me(H)N-	CH ₂	3-thienyl	CH ₂ SCH ₃	Cy*		HCl	653 (80%) ^b 293 (100%)	(CD ₃ OD) ^c 0.92 (d, 3H), 0.96 (d, 3H), 2.13 (s, 1.5H), 2.14 (s, 1.5H), 2.72 (d, 3H), 2.45 (m, 1H), 4.30 (m, 1H), 7.01 (d, 1H), 7.12 (d, 1H), 7.38 (dd, 1H)
197	Me ₂ N-	O	Ph	CH ₂ SCH ₃	Cy*		HCl	663 (100%) ^b 244 (15%)	(CD ₃ OD) ^c 0.91 (d, 3H), 0.93 (d, 3H), 2.80 (dd, 1H), 2.12 (s, 3H), 3.42 (dd, 1H), 4.28 (m, 1H), 4.61 (m, 1H), 5.12 (dd, 1H), 7.28 (m, 5H)

Legend: (a) Cy = Cyclohexyl, (b) obtained on salt, (c) obtained on free base.

The following Examples were synthesized by coupling of the appropriate intermediate with the appropriate intermediate according to general procedure C. If the amine component was a hydrochloride, 1 equiv of triethylamine was employed.



Example	Z	R ₃	R ₄	R ₅	R ₆	FAB-MS M ⁺ +H (%)	¹ H NMR (Partial)
198	NH	p-I-C ₆ H ₄	CH ₃ SMc	Cy ^a	COO <i>i</i> Pr	371 (100) ^b 759 (22)	(CDCl ₃) 0.9 (m, 2H), 1.26 (d, 6H), 2.12 (s, 3H), 3.62 (m, 4H), 4.08 (d, 1H), 5.03 (m, 1H), 6.97 (d, 2H), 7.63 (d, 2H)
199	NH	p-I-C ₆ H ₄	n-Pr	Cy ^a	COO <i>i</i> Pr	741 (27) ^b 371 (100)	(CDCl ₃) 0.88 (t, 3H), 1.26 (d, 3H), 1.27 (d, 3H), 2.40 (m, 4H), 3.00 (dd, 1H), 3.11 (dd, 1H), 4.09 (m, 1H), 6.96 (d, 1H), 7.60 (d, 1H)
200	O	Ph	CH ₃ SMc	Cy ^a		634 (30) ^b 119 (100)	(CDCl ₃) 0.88 (m, 2H), 2.12 (s, 3H), 3.15 (dd, 1H), 3.27 (dd, 1H), 4.42 (d, 1H), 5.31 (dd, 1H), 4.3-4.5 (m, 3H), 5.27 (dd, 1H)

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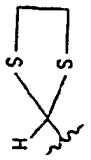
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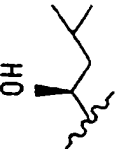

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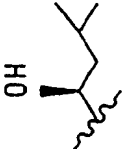
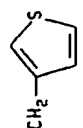
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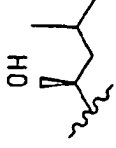
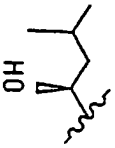
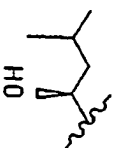
Example	Z	R ₁	R ₂	R ₃	R ₄	R ₅	R ₆	FAB-MS $\overline{M}^+ + H$ (%)	¹ H NMR (Partial)
201	O		Ph		CH ₂ SMc	Cy [*]		652 (42) 119 (100) ^b	(CDCl ₃) 0.87 (m, 2H), 2.10 (s, 3H), 2.4 (m, 4H), 3.07 (m, 4H), 3.72 (m, 4H)

Example	Z	R ₃	R ₄	R ₅	R ₆	FAB-MS M ⁺ + H (%)	¹ H NMR (Partial)
202	O	Ph	CH ₂ SMc		Cy*	666 (25) 126 (100) ^b	(CDCl ₃) 0.9 (m, 2H), 2.0 (m, 2H), 2.1 (br s, 3H), 3.12 (dd, 1H), 3.25 (dd, 1H), 3.7 (m, ca. 4H), 3.81 (d, 1H), 4.4 (m, 1H), 4.53 (m, 1H)
203	O	Cy*	CH ₂ SMc		Cy*	648 (32) 126 (100) ^b	(CDCl ₃) 1.25 (d, 3H), 1.26 (d, 3H), 2.18 (s, 3H), 2.67 (dd, 1H), 2.97 (dd, 1H), 3.33 (d, 1H), 5.02 (m, 1H), 5.08 (t, 1H)
204	O	Cy*	CH ₂ SMc		Cy*	640 (25) 126 (100) ^b	(CDCl ₃) 0.90 (d, 3H), 0.92 (d, 3H), 2.12 (s, 3H), 2.85 (dd, 1H), 4.35 (m, 1H), 4.50 (q, 1H), 4.90 (t, 1H), 6.73 (m, 2H)

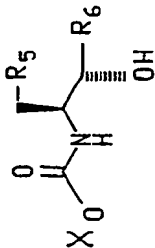
(a) Cy = cyclohexyl (b) M⁺ by chemical ionization

Example	Z	R ₃	R ₄	R ₅	R ₆	FAB-MS M ⁺ +H (%)	¹ H NMR (Partial)
205	NH	p-CH ₃ O- C ₆ H ₄	CH ₂ SMc	Cy*		663 (20) 119 (100)	(CDCl ₃) 0.93 (d, 3H), 0.94 (d, 3H), 2.09 (s, 3H), 2.42 (m, 4H), 3.56 (m, 4H), 3.79 (s, 3H), 4.03 (d, 1H), 4.22 (m, 1H), 4.52 (m, 1H)
206	NH	Ph	CH ₂ SMc	Cy*	CONHMe		(DMSO-d ₆) 2.07 (s, 3H), 2.57 (br, 3H), 3.54 (m, 3H), 3.81 (br, 1H), 4.12 (br, 1H), 4.42 (m, 2H)
207	NH	p-CH ₃ O- C ₆ H ₄	CH ₂ C=CH ₂	Cy*	COO ⁱ Pr	643 (40) 275 (100)	(CDCl ₃) 1.26 (d, 3H), 1.27 (d, 3H), 2.94 (dd, 1H), 3.13 (dd, 1H), 3.77 (s, 3H), 4.08 (dd, 1H), 5.6 (m, 1H), 6.84 (d, 2H), 7.12 (d, 2H)
208	O	Ph	CH ₂ SMc	Cy*		634 (50) 119 (100)	(CDCl ₃) 0.92 (d, 3H), 0.94 (d, 3H), 2.07 (s, 3H), 2.61 (dd, 1H), 3.72 (q, 1H), 4.32 (m, 1H), 4.45 (q, 1H), 5.10 (dd, 1H), 7.3 (m)

Example	Z	R ₁	R ₂	R ₃	R ₄	FAB-MS M ⁺ +H (%)	¹ H NMR (Partial)
209	CH ₂	Ph		Cy*	CH ₂ SCMe 	632 (45) 272 (100)	CDCl ₃ , 0.86 (d, 3H), 0.91 (d, 3H), 2.11 (s, 3H), 3.61 (t, 2H), 3.83 (t, 2H), 4.33 (m, 1H), 4.43 (q, 1H), 6.7 (d, 1H), 6.85 (d, 1H)
210	CH ₂		p-I-C ₆ H ₄	Cy*	CH ₂ SCH ₃	758 (40%) 397 (100%)	(CDCl ₃) 1.22 (d, 6H), 1.85 (d, 1H), 2.91 (dd, 1H), 4.09 (d, 1H), 4.33 (q, 1H), 4.50 (m, 1H), 6.94 (d, 2H), 7.62 (d, 2H)
211	CH ₂		2-thienyl	Cy*	CH ₂ SCH ₃	638 (35%) 278 (100%)	(CDCl ₃) 0.90 (m, 2H), 1.20 (d, 6H), 1.82 (m, 1H), 2.63 (dd, 1H), 3.30 (m, 1H), 4.30 (m, 1H), 5.00 (m, 1H), 6.80 (d, 1H), 6.87 (dd, 1H), 7.12 (d, 1H)
212	NH		Ph	Cy*		669 (45%) 245 (100%)	(CDCl ₃) 1.22 (d, 3H), 1.24 (d, 3H), 1.81 (d, 1H), 2.92 (dd, 1H), 3.01 (dd, 1H), 3.18 (dd, 1H), 3.27 (dd, 1H), 4.07 (dd, 1H), 4.53 (m, 1H)

Example	Z	R ₁	R ₂	R ₃	R ₄	FAB-MS M ⁺ +H (%)	¹ H NMR (Partial)
213	NH	Ph	CH ₂ C=CH	Cy		613 (45%) 245 (100%)	(CDCl ₃) 0.93 (d, 3H), 0.94 (d, 3H), 2.68 (m, 1H), 2.91 (dd, 1H), 3.17 (m, 1H), 4.12 (m, 1H), 4.28 (m, 1H), 4.90 (d, 1H), 5.12 (m, 2H)
214	CH ₂	3-thienyl	CH ₂ SCH ₃	Cy		638 (27%) 278 (100%)	(CDCl ₃) 0.92 (d, 3H), 0.93 (d, 3H), 2.01 (s, 3H), 3.43 (t, 2H), 4.27 (m, 1H), 4.50 (m, 1H), 6.99 (dd, 1H), 7.08 (d, 1H), 7.31 (dd, 1H)
215	CH ₂	2-thienyl	CH ₂ SCH ₃	Cy		638 (40%) 278 (100%)	(CDCl ₃) 2.12 (s, 3H), 3.38 (dd, 1H), 3.67 (t, 2H), 3.81 (t, 2H), 4.32 (m, 1H), 4.43 (m, 1H), 6.76 (dd, 1H), 6.82 (d, 1H), 6.93 (dd, 1H)

According to the procedure described by Luly et al (J. Org. Chem. 53, 6109, (1988)) with the substitution of the appropriate Grignard reagent, the following compounds were prepared



Example	R ₅	R ₆	FAB-MS M ⁺ +H (%)	¹ H NMR (Partial)
216	Cyclohexyl			(CDCl ₃) 1.45 (s, 9H), 2.22 (m, 1H), 2.36 (m, 1H), 3.37 (m, 2H), 4.05 (m, 1H), 4.30 (d, 1H), 4.53 (d, 1H), 5.01 (m, 2H), 5.82 (m, 1H)
217	Cyclohexyl		370 (15%) 270 (100%)	(CDCl ₃) 1.44 (s, 9H), 2.12 (m, 1H), 3.21 (m, 1H), 3.32 (m, 1H), 4.05 (m, 1H), 4.22 (d, 1H), 4.57 (d, 1H)
218	Cyclohexyl		356 (30%) 256 (100%)	(CDCl ₃) 1.43 (s, 9H), 2.01 (d, 1H), 2.12 (m, 2H), 3.33 (m, 2H), 4.07 (m, 1H), 4.32 (d, 1H), 4.60 (d, 1H), 5.00 (m, 2H), 5.73 (m, 1H)

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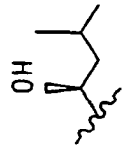
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Example	R ₂	R ₃	FAB-MS M ⁺ +H (%)	¹ H NMR (Partial)
219	2-thienyl			(CDCl ₃) 0.86 (d, 3H), 0.91 (d, 3H), 1.42 (s, 9H), 1.89 (m, 1H), 2.08 (d, 1H), 3.09 (d, 2H), 3.27 (m, 1H), 3.34 (m, 1H), 3.92 (d, 1H), 4.17 (m, 1H)

55 Example - 220

2S-(2(S)-N-t-BOC-amino-3-cyclohexyl-1(R)-hydroxy)prop-1-yl-5(R)-methyltetrahydrofuran

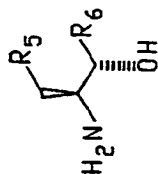
The compound of example 216 (870 mg) was dissolved in 14 mL of CH₂Cl₂ and 14 ml of saturated sodium bicarbonate. The solution was cooled to 0 °C, and iodine (680 mg) was added in one portion. After stirring for 30 minutes, sodium bisulfite was added, and then 50 mL of ether. The organic layer was washed with saturated sodium bicarbonate, brine, dried (MgSO₄) and concentrated and purified by flash chromatography (Amicon matrix silica SI (trademark), 30 μM) to give 1.01 g of the primary iodide. This material (150 mg) was dissolved in 1.5 mL of 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone, and 24 mg of NaBH₄ was added. After stirring at 25 °C for 5 days, the mixture was diluted with ether, washed with water (3X), brine dried (MgSO₄) and concentrated. Purification by flash chromatography (Amicon matrix silica SI (trademark), 30 μM) provided 101 mg of the title compound. ¹H NMR (CDCl₃, 300 MHz, partial) δ 0.90 (m, 2H), 1.23 (d, 3H), 1.52 (s, 9H), 2.10 (m, 1H), 2.81 (d, 1H), 3.62 (m, 1H), 3.69 (m, 1H), 4.04 (m, 1H), 4.83 (d, 1H).

Example - 221

2S-(2(S)-amino-3-cyclohexyl-1(R)-hydroxy)prop-1-yl-5(R)-methyltetrahydrofuran

The product of the preceding Example (160 mg) was deprotected according to procedure D to yield 130 mg of the title compound.

According to Procedure D, the following analogues were prepared from the corresponding N-t-Boc derivatives.



Example	R ₅	R ₆	Salt Form	FAB-MS M ⁺ +H (%)	¹ H NMR (Partial)
222	Cyclohexyl		HCl		(CD ₃ OD) 2.15 (m, 2H), 2.32 (m, 1H), 2.92 (m, 1H), 3.17 (dt, 1H), 3.22 (dd, 1H), 3.55 (m, 1H), 4.12 (m, 1H), 5.00 (m, 2H), 5.87 (m, 1H)
223	Cyclohexyl		HCl	270 (100%) 126 (15%)	(D ₂ O) 3.47 (m, 1H), 3.68 (m, 1H), 3.97 (m, 1H), 5.24 (m, 1H)
224	Cyclohexyl		HCl	256 (100%) 126 (20%)	(CDCl ₃) 0.93 (m, 2H), 1.72 (m, 6H), 2.11 (m, 2H), 3.20 (t, 1H), 3.38 (dd, 1H), 3.73 (m, 1H), 5.00 (m, 2H), 5.81 (m, 1H)

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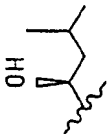
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Example	R_5	R_6	Salt Form	FAB-MS $M^+ + H$ (%)	1H NMR (Partial)
225	2-thienyl		HCl		(D ₂ O) 0.86 (d, 3H), 0.88 (d, 3H), 1.20 (m, 2H), 1.60 (m, 1H), 3.13 (dd, 1H), 3.23 (m, 2H), 3.70 (m, 1H), 7.00 (d, 2H), 7.32 (dd, 1H)

Example - 226

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SMeCys-2(S)-amino-1-cyclohexyl-(3(R),4(S)-dihydroxy-5-cyclopentyl)pentanea) BOC-SMeCys-2(S)-amino-1-cyclohexyl-(3(R), 4(S))-dihydroxy-5-cyclopentyl)pentane

BOC-SMeCys (254 mg) and 2S-amino-1-cyclohexyl-(3R, 4S)-dihydroxy-5-cyclopentyl-pentane (300 mg) were coupled according to procedure C, and the product purified by crystallization from isopropyl ether/hexanes to give 254 mg of the title compound. ¹H NMR (CDCl₃, 300 MHz, partial) δ 1.44 (s, 9H), 2.03 (m, 1H), 2.15 (s, 3H), 2.25 (m, 1H), 2.82 (d, 2H), 3.25 (m, 2H), 4.09 (m, 1H), 4.23 (q, 1H), 4.39 (dt, 1H), 5.37 (d, 1H), 6.43 (d, 1H).

b) SMeCys-2(S)-amino-1-cyclohexyl-(3(R),4(S))-dihydroxy-5-cyclopentylpentane

BOC-SMeCys-2S-amino-1-cyclohexyl-(3(R),4(S))-dihydroxy-5-cyclopentyl-pentane (245 mg) was dissolved in 2 mL of CH₂Cl₂ and cooled to 0 °C. Trifluoroacetic acid (2.5 mL) was added, and the reaction stirred at 0 °C for 1 h. The mixture was concentrated and the residue dissolved in ethyl acetate and extracted with 0.5N NaOH, brine, dried (Na₂SO₄) and concentrated to give 173 mg of the title compound.

Example - 227

SMeCys-2(S)-amino-1-(2-thienyl)-(3(R), 4(S))-dihydroxy-6-methylheptane

2S-amino-1-(2-thienyl)-(3(R), 4(S))-dihydroxy-6-methylheptane (163 mg) was coupled with BOC-SMeCys according to procedure C and deprotected according to the procedure of Example 226B to give the title compound (117 mg). ¹H NMR (CDCl₃, 300 MHz, partial) δ 0.86 (d, 3H), 0.93 (d, 3H), 1.99 (s, 3H), 2.42 (dd, 1H), 2.91 (dd, 1H), 3.40 (d, 1H), 3.57 (dd, 1H), 4.40 (m, 1H), 6.81 (d, 1H), 6.92 (dd, 1H), 7.18 (d, 1H), 7.70 (d, 1H).

Example 228

SMeCys-8(S)-amino-9-cyclohexyl-(6(S),7(R))-dihydroxy-1-nonene

8(S)-amino-9-cyclohexyl-(6(S), 7(R))-dihydroxy-1-nonene (142 mg) was coupled with BOC-SMeCys according to Procedure C and the product deprotected according to the procedure of Example 226B to give the title compound (94 mg). ¹H NMR (CDCl₃, 300 MHz, partial) δ 1.00 (m, 2H), 2.73 (dd, 1H), 2.98 (dd, 1H), 3.18 (t, 1H), 3.26 (d, 1H), 3.62 (dd, 1H), 4.28 (dd, 1H), 4.60 (m, 1H), 5.01 (m, 2H), 5.82 (m, 1H), 7.50 (d, 1H). FAB MS 373 (MH⁺).

Example - 229

4-(4-piperidone)-2(R)-(2-thienylmethyl)succinate

2(R)-(2-thienylmethyl)-succinnic acid 1-monobenzyl ester was prepared by adapting the procedure described by Plattner et al. (J. Med. Chem. 31, 2277, (1988)) to 3-(2-thienyl) propionic acid, coupled with 4-piperidone monohydrate according to Procedure C, and the monoamide/mono-ester product hydrogenated according to the procedure of Example 125 to give the title compound. ¹H NMR (CDCl₃, 300 MHz, partial) δ 2.56 (dd, 1H), 2.79 (dd, 1H), 3.12 (dd, 1H), 3.91 (m, 1H), 6.82 (d, 1H), 6.90 (dd, 1H), 7.13 (d, 1H).

Example - 230

4-(4-piperidone)-2(R)-(4-iodophenylmethyl)-succinate

2(R)-(4-iodophenylmethyl)-succinnic acid 1-monobenzyl ester was prepared by adapting the procedure described by Plattner et al. (J. Med. Chem., 31, 2277, (1988)) to 3-(4-iodophenyl) propionic acid, coupled with 4-piperidone monohydrate according to Procedure C, and the product hydrogenated according to the procedure of Example 125 to give the title compound. ¹H-NMR (CDCl₃, 300 MHz, partial) δ 2.70 (m, 2H), 3.12 (dd, 1H), 3.23 (m, 1H), 3.60 (m, 1H), 3.73 (m, 2H), 3.99 (m, 1H), 6.91 (d, 2H), 7.60 (d, 2H).

Example - 231

4-(4-piperidone)-2R-(3-thienylmethyl)-succinate

2(R)-(3-thienylmethyl)-succinnic acid 1-monobenzyl ester was prepared by adapting the procedure

described by Plattner et al. (J. Med. Chem., 31, 2277, (1988)) to 3-(3-thienyl) propionic acid, coupled with 4-piperidone monohydrate according to Procedure C, and then hydrogenated according to the procedure of Example 125 to give the title compound. ¹H NMR (CDCl₃, 300 MHz, partial) δ 2.73 (dd, 1H), 2.88 (dd, 1H), 3.16 (dd, 1H), 3.22 (m, 1H), 3.95 (m, 1H), 6.90 (dd, 1H), 6.99 (d, 1H), 7.27 (dd, 1H).

5

Example - 232

4-(4-Trimethylammonio-1-piperidino)-2R-benzylsuccinate-SMeCys-norCSta Isopropyl Ester Iodide

10 4-(4-Dimethylamino-1-piperidino)-2R-benzylsuccinate-SMeCys-norCSta Isopropyl Ester (420 mg) was converted to the title compound (320 mg) according to the procedure described in Example 38. ¹H NMR (CDCl₃, 300 MHz, partial) δ 1.23 (d, 6H), 2.10 (s, 1.5H), 2.12 (s, 1.5H), 3.07 (s, 4.5H), 3.09 (s, 4.5H), 3.60 (m, 1H), 4.67 (m, 1H), 5.00 (m, 1H). FAB MS 675 (M⁺), 256.

Example 233

S-Methylcysteine t-Butyl ester hydrochloride.

A mixture of 13.5 g S-methylcysteine, 120 mL dioxane, and 10 mL concentrated sulfuric acid was cooled to 0 °C and isobutylene (ca. 50 mL) was added. The vessel was sealed and the mixture shaken at 25 °C for 16 hours and poured into a mixture of ethyl acetate, ice, and 80 mL of 6N NaOH. The layers were separated and the aqueous layer extracted with ethyl acetate. The organic layers were washed with brine, dried, and concentrated giving 8.5 g of a yellow oil. Ether (110 mL) was added, followed by 9 mL of 4M HCl-dioxane. The resulting solid was filtered and washed with ether giving the title substance as a colorless solid. ¹H NMR (D₂O, partial) δ 1.53 (s, 9H), 2.18 (s, 3H), 3.09 (dd, 1H), 3.16 (dd, 1H), 4.28 (dd, 1H).

25

4-(4-Dimethylaminopiperidino)-2(R)-benzylsuccinoyl-SMeCys t-Butyl ester

4-(4-Dimethylaminopiperidino)-2(R)-benzylsuccinic acid hydrochloride (5.97 g) and S-methylcysteine t-butyl ester hydrochloride were coupled and according to General Procedure C giving 2.97 g of the title substance as a clear oil. FAB-MS 492 (100%, M⁺ + H). ¹H NMR 1.38 and 1.39 (s, 9H total), 2.05 (s, 3H), 2.19 and 2.20 (s, 6H total), 3.80 (m, 2H), 4.55 (m, 2-3H), 7.1-7.3 (m, 5H).

30

Example 235

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4-(4-Dimethylaminopiperidino)-2(R)-benzylsuccinoyl-SMeCys Hydrochloride

2.67 Grams of 4-(4-dimethylaminopiperidino)-2(R)-benzylsuccinoyl-SMeCys t-butyl ester was converted to the title substance, (2.98 g) by General Procedure D. ¹H NMR (D₂O, partial) δ 2.09 and 2.10 (s, 3H total), 2.84 (s, 6H total), 7.24-7.40 (m, 5H).

40

Example 236

4-(1-piperidino)piperidine-1-carbonyl-Phe Benzyl Ester

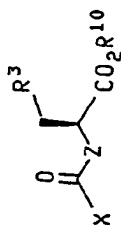
45

A solution of phenylalanine benzyl ester (10 mmol) in 15 ml dichloromethane was added dropwise to a 0 °C solution of 1.34 g imidazole and 1.75 g carbonyldiimidazole in dichloromethane (15 ml), and the mixture was stirred at 25 °C for 1 hour. 2.27 g of 4-(1-piperidino)piperidine was added and the mixture was stirred 24 hours, diluted with ethyl acetate, the solution extracted with 1N NaOH and brine, dried and concentrated giving an oil which was chromatographed on silica eluting with an ethanol-dichloromethane gradient containing triethylamine to give 3.69 g of the title substance as an oil. FAB-MS 450 (100%, M⁺ + H). ¹H NMR (CDCl₃, partial) δ 3.10 (d, 2H), 3.90 (m, 2H), 4.83 (m, 2H), 5.10 (d, 1H), 5.17 (d, 1H), 7.2-7.4 (m, 10H).

50

Using the above procedure, the following Examples were also prepared from the appropriate amino acid ester or substituted lactic acid ester and the appropriate secondary amine. One or both of the amine components could also be in an acid addition salt form, in which case one equivalent of triethylamine per equivalent of acid addition salt was additionally employed.

55



Example	X	Z	R ₃	R ₁₀	MS	¹ H NMR (CDCl ₃ , partial), δ
237		NH	p-I-C ₆ H ₄	t-Bu	473 (100)	1.42 (s, 9H), 2.45 (m, 4H), 3.05 (m, 2H), 3.65 (t, 4H), 4.68 (m, 1H), 6.90 (d, 2H), 7.58 (d, 2H).
238		O	Cyclohexyl	CH ₃	312 (100)	
239		NH	Cyclohexyl	CH ₂ Ph	387 (100)	2.47 (t, 4H), 3.69 (m, 4H), 4.61 (m, 1H), 4.92 (d, 1H), 5.08 (d, 1H), 5.22 (d, 1H), 7.34 (m, 5H).

Example 240

Hexahydrophenylalanine benzyl ester hydrochloride

A solution of Boc-hexahydrophenylalanine (10 g) and triethylamine in 85 ml dichloromethane (5.4 mL) was treated sequentially at <5 °C with benzyl chloroformate (5.5 mL) and dimethylaminopyridine (450 mg). After being stirred 30 minutes at 25 °C the mixture was diluted with 500 mL dichloromethane and the resulting solution extracted with aqueous NaHCO₃, 1N HCl, 1N NaOH, brine, dried, and concentrated giving 12.2 g of a colorless oil. This material was dissolved in 15 mL dichloromethane and treated at 25 °C with 95

mL 4.7 M HCl-dioxane for 1 hour, concentrated, and the resulting solid washed with ether giving 9.25 g of the title substance as a colorless solid.

Example 241

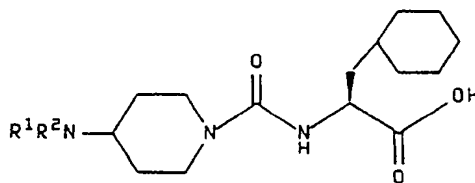
4-Ketopiperidine-1-carbonyl-hexahydrophenylalanine

A solution of the benzyl ester of the title substance (4.45 g) in 40 mL methanol and 4 mL acetic acid was shaken with 450 mg 10% palladium on carbon under 50 p.s.i. hydrogen for 20 minutes. The catalyst was filtered, the filtrate concentrated, and the residue dissolved in ethyl acetate. This solution was washed with water (3X), dried, and concentrated giving the title substance (3.41 g) as a colorless foam. ^1H NMR (CDCl_3 , partial) δ 2.50 (t, 4H), 3.71 (m, 4H), 4.45 (m, 1H), 5.19 (d, 1H), and 7.6 (br, 1H). FAB-MS 297 (100%, $\text{M}^+ + \text{H}$).

Example 242

4-(1-Pyrrolidino)piperidine-1-carbonyl-hexahydro-L-phenylalanine

A solution of 4-(1-pyrrolidino)piperidine-1-carbonyl-L-Phe (1.5 g) in 20 mL aqueous 0.22 M HCl was shaken with 1 g 10% rhodium on carbon under 50 p.s.i. hydrogen pressure for 3 hours. The catalyst was filtered, the filtrate concentrated, and the residue washed with ether and dried giving the title substance as a colorless solid (1.07 g), RP-HPLC 4.76 minutes (30/70, 100%). In analogous fashion the following compounds were also prepared.



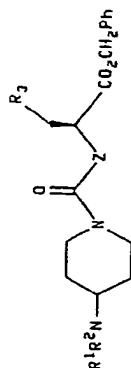
Example	$\text{R}_1\text{R}_2\text{N}$	FAB-MS	^1H NMR (D_2O , partial)
243		366 (100)	0.95 (m, 2H), 2.95 (m, 2H), 4.1 (m, 2H), 4.28 (m, 1H).
244	$(\text{CH}_3)_2\text{N}$	326 (100)	2.84 (s, 3H), 3.47 (m, 1H), 4.13 (d, 2H), 4.26 (t, 1H).
245	Et_2N		1.41 (t, 6H), 2.18 (d, 2H), 3.02 (t, 3H), 3.2-3.5 (m, 4H), 3.7 (m, 1H), 4.22 (m, 2H), 4.4 (t, 1H).

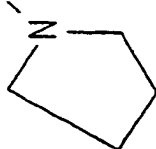
Example 246

4-(1-Pyrrolidino)piperidine-1-carbonyl-L-phenylalanine Benzyl ester

4-Ketopiperidine-1-carbonyl-L-phenylalanine benzyl ester (US 4,314,342) was reductively aminated with pyrrolidine according to general procedure A (above) and purified by chromatography in an ethanol-dichloromethane gradient giving the title substance as a colorless solid (3.8 g). FAB-MS 410 ($M^+ + H$, 100%), 1H NMR ($CDCl_3$, partial) δ 2.54 (m, 4H), 2.81 (dq, 2H), 3.09 (d, 2H), 3.82 (dm, 2H), 4.85 (m, 1H), 5.17 (d, 1H ea.), 6.98 (m, 2H), 7.15-7.4 (m, ca 10H).

In analogous fashion to Example 246, the following compounds were also prepared.

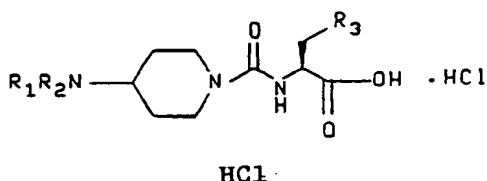


Example	R_1R_2N	Z	R_3	FAB-MS $M^+ + H$ (%)	1H NMR ($CDCl_3$, partial) δ
247	Me_2N	NH	Ph	410 (100)	2.25 (s, 6H), 2.73 (m, 2H), 3.09 (d, 2H), 3.90 (m, 2H), 4.83 (t, 1H), 4.86 (t, 1H), 5.09 (d, 1H), 5.16 (d, 1H), 7.15-7.4 (m, 10H).
248	Et_2N	NH	Ph	438 (100)	1.01 (t, 6H), 2.51 (q, 9H), 3.09 (m, 2H), 3.90 (m, 2H), 4.85 (m, 2H), 5.09 (d, 1H), 5.17 (d, 1H).
249		NH	Ph	436 (100)	2.82 (dq, 2H), 2.99 (d, 2H), 3.78 and 3.88 (dt, 1H ea.), 4.84 (m, 2H), 5.09 (d, 1H), 5.16 (d, 1H), 6.99 (m, 2H), 7.15-7.4 (m, 10H).
250	Me_2N	NH	p- $CH_3O-C_6H_4$	440 (100)	2.34 (s, 6H), 3.03 (d, 2H), 3.75 (s, 3H), 3.93 (m, 2H), 4.75 (m, 1H), 4.87 (d, 1H), 5.07 and 5.17 (d, 1H ea.), 6.73 and 6.88 (d, 2H ea.).

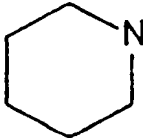
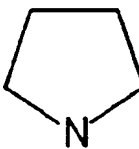
Example 251

4-(1-Pyrrolidino)piperidine-1-carbonyl-L-phenylalanine

5 4-(1-Pyrrolidino)piperidine-1-carbonyl-L-phenylalanine benzyl ester (3.7 g) was dissolved in 15 mL water containing 1.1 equivalent 1N HCl and the resulting solution shaken with 375 mg 10% palladium on carbon for 1 hour. Filtration and concentration gave a residue which was washed with ether and dried giving the title substance as a colorless solid (2.79 g). FAB-MS 343 ($M^+ + H$, 40%), 155 (60%), 11.9 (100%). 1H NMR (D_2O , partial) δ (DSS) 1.4 (m, 2H), 3.02 (dd, 1H), 3.25 (dd, 1H), 3.6 (m, 2H), 3.95 (t, 2H), 4.50 (dd, 1H), 7.25-7.4 (m, 5H). In analogous fashion, the following hydrochlorides were also prepared from the corresponding benzyl esters.



20

Example	R_1R_2N	R_3	FAB-MS Base, $M^+ + H$ (%)	1H NMR (partial, D_2O)
252		Ph	368 (10) 155 (100)	2.99 (dd, 1H), 3.25 (dd, 1H), 3.46 (dd, 1H), 3.95 (t, 2H), 4.54 (dd, 1H), 7.25-7.4 (m, 5H)
253	$(CH_3)_2N$	Ph	320 (30) 119 (100)	2.81 (s, 6H), 3.02 (dd, 1H), 3.27 (dd, 1H), 4.0 (t, 2H), 7.25-7.45 (m, 5H).
254	Et_2N	Ph		1.33 (t, 6H), 1.95 (d, 2H), 3.97 (t, 2H), 4.56 (dd, 1H), 7.3-7.5 (m, 5H).
255		Ph	346 (40) 119 (100)	3.02 (dd, 1H), 3.23 (dd, 1H), 3.58 (m, 2H), 3.95 (m, 2H), 4.50 (dd, 1H), 7.2-7.4 (m, 5H).

Example 256

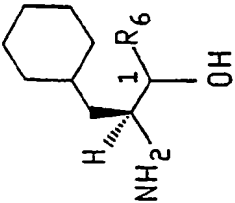
1(S) and 1(R) 2(S)-Amino-3-cyclohexyl-1-(2-thiazolyl)-1-propanol

55 Using the procedure of Ryono and Weller (EP 337 295/EP 341481), 2(S)-(Butoxycarbonylamino)-3-cyclohexyl-1-propanal was condensed with 2-lithiothiazole and the product purified by chromatography on silica gel in ethyl acetate-hexane without separation of the isomers, giving the Boc analogs of the title

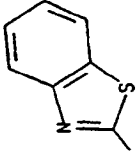
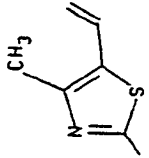
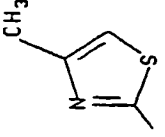
substances in 66% yield. This mixture was deprotected with HCl-dioxane according to Procedure D and the product further converted to the free base (97%) by partitioning between 1N NaOH/ethyl acetate, and separation, drying, and concentration of the organic layer. 5.85 Grams of this mixture was chromatographed on 200 g silica gel packed in 1:1:200 concentrated $\text{NH}_4\text{OH}/\text{EtOH}/\text{CH}_2\text{Cl}_2$ and eluted with 1L each of 1:1:200, 1:2:200, 1:4:200, 1:8:200 and 1:16:200 concentrated $\text{NH}_4\text{OH}/\text{EtOH}/\text{CH}_2\text{Cl}_2$.

The faster moving (less polar) isomer (3.2 g), and the slower moving/more polar isomer (0.57 g) and a mixture (1.75 g) were obtained. Less Polar isomer: ^1H NMR (CDCl_3 , partial) δ 3.41 (m, 1H), 4.64 (d, 1H, $J = 3.4$ Hz), 7.25 (d, 1H, $J = 3.2$ Hz), 7.71 (d, 1H, $J = 3.2$ Hz). More polar isomer: ^1H NMR (CDCl_3 , partial) δ 3.28 (m, 1H), 4.87 (d, 1H, $J = 3.2$ Hz), 7.25 (d, 1H, $J = 3.2$ Hz), 7.71 (d, 1H, $J = 3.2$ Hz). These substances were separately converted to their corresponding N-t-Boc derivatives the TLC behavior of which was compared: The less polar title substance gave the less polar Boc derivative and was thus assumed to have 2 (S), 1(R) stereochemistry since this the less polar Boc derivative is purported to have this stereochemistry (EP 337295).

By this procedure, the following compounds were also prepared.



Example	R ₆	Isomer at Position 1'	FAB-MS M ⁺ H (%)	¹ H NMR (CDCl ₃ , partial)
257	<chem>Cc1ccsc1</chem>	less polar	255 (100)	2.41 (d, 3H), 3.31 (dt, 1H), 4.55 (d, 1H), 7.32 (d, 1H).
258		more polar	255 (100)	2.41 (d, 3H), 3.22 (m, 1H), 4.74 (d, 1H), 7.32 (d, 1H).
259 ..	<chem>Cc1cc(C)sc1</chem>	less polar	269 (100)	2.24 (s, 3H), 2.29 (s, 3H), 3.25 (m, 1H), 4.52 (d, 1H).
260		more polar	269 (100)	2.23 (s, 3H), 2.28 (s, 3H), 3.23 (m, 1H), 4.75 (d, 1H).

Example	R ₆	Isomer at Position 1 ^a	FAB-MS M ⁺ +H (%)	¹ H NMR (CDCl ₃ , partial)
261		less polar	291 (100)	3.49 (m, 1H), 4.74 (d, 1H), 7.35 (dt, 1H), 7.43 (dt, 1H), 7.85 (d, 1H), 7.94 (d, 1H).
262		less polar	281 (100)	2.36 (s, 3H), 3.32 (m, 1H), 4.52 (d, 1H), 5.17 (d, 1H), 5.39 (d, 1H), 6.71 (dd, 1H).
263		less polar	255 (100)	2.38 (d, 3H), 3.32 (dt, 1H), 4.58 (d, 1H), 6.78 (d, 1H).
264		more polar	255 (100)	2.37 (d, 3H), 3.23 (m, 1H), 4.79 (d, 1H), 6.77 (d, 1H).

a, by TLC in 18/2/1 CHCl₃ /EtOH/conc. NH₄OH. Less polar = faster moving isomer.

Example 265

2(S)-[4-(4-Dimethylaminopiperidino)-2(R)-benzylsuccinoyl-S-methylcysteinylamino]-3-cyclohexyl-1(R)-(2-imidazolyl)-1-propanol

The compound of example 148 (119 mg) was shaken under 50 p.s.i. hydrogen pressure with 200 mg 20% Pd(OH)₂ on carbon catalyst in 10 ml water containing 0.34 mL 1N HCl for 24 hours. Filtration, concentration, and trituration with ether gave the title substance as the dihydrochloride (65 mg): FAB-MS 641 (M⁺ + H, 20%), 309 (20), 155 (65), 119 (100).

Example 266

2 (S)-[4-(4-Dimethylaminopiperidino)-2(R)-benzylsuccinoyl-S-methylcysteinylamino]-3-cyclohexyl-1(S)-(2-imidazolyl)-1-propanol

By the procedure of the preceding example the compound of Example 104 was converted to the title substance. FAB-MS 641 (M⁺ + H, 100%). ¹H NMR (CDCl₃, partial) δ 2.04 and 2.06 (s, 3H total), 2.21 and 2.23 (s, 6H total), 3.62 (m, 2H), 4.35 (m, ca. 3H), 4.44 (m, 1H), 4.7 (d, 1H).

Example 267

4(S)-cyclohexylmethyl-5(R)-isopropoxycarbonyl oxazolidone

Nor-CSta isopropyl ester (30 g) was added in one portion to a stirred 25 °C solution of 30 g carbonyldiimidazole in 250 mL dichloromethane. After 1 hour the solution was washed twice with 300 mL portions of 2N HCl and twice with 300 mL portions of 2N NaOH, brine, dried, concentrated, and the residue chromatographed on silica (500 g) eluted with 1:3 ethyl acetate hexanes giving 23.6 g of the title substance. ¹H NMR (CDCl₃, partial) δ 1.26 and 1.27 (d, 3N ea), 3.90 (m, 1H), 4.49 (d, 1H), 5.11 (m, 1H), 5.61 (br, 1H).

Example 268

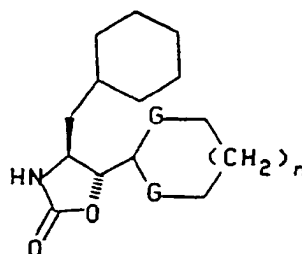
4(S)-cyclohexylmethyl-5(R)-formyl-2-oxazolidone

A solution of 28.1 g 4(S)-cyclohexylmethyl-5(R)-isopropoxycarbonyl-2-oxazolidone in 500 mL anhydrous toluene was treated at -78 °C over 20 minutes with 250 mL of a 2.4 M solution of diisobutylaluminum hydride in hexane. After 15 minutes, 50 mL methanol was added dropwise at -78 °C, followed by 500 ml of 50% aqueous Rochelle salts and 500 ml ether. The ether layer was separated at 25 °C and the aqueous layer extracted twice with 500 ml ether. The organic layers were combined, washed with brine, dried, and concentrated giving (13.9 g, TLC RF 0.23 in ethyl acetate/ silica) a yellow foam which was used without further purification. The compound, which streaked on the TLC plate, was characterized as being the title substance by clean conversion to various expected products as described below, and to a single, well-behaved slightly less polar compound believed to be the corresponding alcohol on treatment with NaBH₄. The title substance gave the following spectrum: ¹³C NMR (CDCl₃, partial major peaks) δ 25.91, 25.97, 26.02, 26.06, 26.37, 32.72, 33.50, 33.55, 33.90, 33.96, 43.55, 43.91, 50.18, 51.55, 55.22, 55.49, 82.62, 83.36, 96.19, 97.04, 159.46, 159.67.

Example 269

4(S)-Cyclohexylmethyl-5(R)-(2-(1,3-dioxolanyl))-2-oxazolidone

The compound of the preceding Example (0.38 g) was heated at reflux in benzene (10 mL) with 23 mg p-toluenesulfonic acid and 0.2 ml ethylene glycol in an apparatus where the condensate was allowed to drip through 3 angstrom molecular sieves before returning to the reaction vessel. After 18 hours, the mixture was cooled, diluted with ethyl acetate, and the resulting solution washed with 1N NaOH, dried, and the residue chromatographed on silica eluting with 1:1 ethyl acetate-hexanes giving the title substance as a colorless solid (290 mg). ¹H NMR (CDCl₃, partial) δ 3.81 (dt, 1H), 3.9-4.15 (m, 4H), 5.00 (d, 1H), 5.82 (br, 1H). In like fashion the following substances were also prepared, substituting the appropriate dithiol or 1,3-dihydroxy propane for ethylene glycol.



Example	G	N	FAB-MS M ⁺ + H (%)	¹ H NMR (CDCl ₃ , partial) δ
270	O	1	270 (100)	3.95 (dt, 1H), 4.70 (d, 1H)
271	S	1	119 (100) 302 (15)	3.90 (m, 1H), 4.01 (d, 1H), 4.40 (t, 1H), 5.44 (s, 1H)
272	S	0	170 (100) 288 (25)	3.24 (d, 4H), 4.15 (dd, 1H) 4.61 (d, 1H), 5.68 (br, 1H)

Example 2732(S)-Amino-3-cyclohexyl-1-(R)-(2-(1,3-dioxolanyl))-1-propanol

4(S)-Cyclohexylmethyl-5(R)-(2-(1,3-dioxolanyl))-2-oxazolidone (168 mg) and barium hydroxide octahydrate (417 mg) were heated at reflux in 5 ml dioxane and 3 ml water for 2 hours. The mixture was filtered and the solids washed with dioxane. The filtrate was concentrated and the residue dissolved in 20 ml ethyl acetate. The resulting solution was washed with water, dried, and concentrated giving a solid which was triturated with hexane give 170 mg of the title substance. ¹H NMR (CDCl₃, partial) δ 3.11 (m, 1H), 3.37 (t, 1H), 3.89 (m, 2H), 4.01 (m, 2H), 4.87 (d, 1H).

Example 2742(S)-Amino-3-cyclohexyl-1-(R)-(2-(1,3-dioxanyl))-1-propanol

By the procedure of the preceding Example, 840 mg of 4(S)-cyclohexylmethyl-5(R)-2-(1,3-dioxanyl))-2-oxazolidone gave 620 mg of the title substance. FAB-MS 244 (M⁺ + H, 100%). ¹H NMR (CDCl₃, partial) δ 3.15 (m, 1H), 3.28 (dd, 1H), 3.7-3.8 (m, 2H), 4.10 (m, 2H), 4.57 (d, 1H).

Example 2752(S)-Amino-3-cyclohexyl-1-(R)-(2(1,3-dithianyl))-1-propanol

A solution of 4(S)-Cyclohexylmethyl-5(R)-(2-(1,3-dithianyl))-2-oxazolidone (480 mg) in 25 ml acetonitrile was treated at 25° C with di-t-butylidicarbonate (450 mg) and 4-dimethylaminopyridine (19 mg). After 21 hours the mixture was diluted with 150 ml ethyl acetate and the resulting solution washed with 50 ml 1N NaOH, brine, dried and concentrated. The residue was chromatographed on silica eluting with ethyl acetate-hexane, giving N-t-Boc oxazolidone (FAB-MS 346 (M⁺ + H, 100%)). This substance was dissolved in 6 ml THF and treated with 1.8 ml of 2N NaOH and 3 ml water. After 24 hours the mixture was diluted with ethyl acetate and the resulting solution washed with brine, dried and concentrated. The residue was chromatographed on silica eluting with ethyl acetate-hexanes giving 2(S)-Boc amino-3-cyclohexyl-1-(R)-(2-1,3-dithianyl))-1-propanol (300 mg, FAB-MS 376 (M⁺ + H, 25%)). This substance was dissolved in 3 ml trifluoroacetic acid at 0° C and the solution stirred at 25° C for 30 minutes, evaporated, and the residue dissolved in dichloromethane. The resulting solution was washed with 1N NaOH, brine, dried, and concentrated giving 184 mg of the title substance as an off white solid. FAB-MS 276 (M⁺ + H, 100%). ¹H

NMR (CDCl₃, partial) δ 3.28 (m, 1H), 3.58 (dd, 1H), 4.11 (d, 1H).

Example 276

5 2(S)-Amino-3-cyclohexyl-1(R)-(2-(1,3-dithiolanyl))-1-propanol

By the same sequence of the preceding Example, 4(S)-cyclohexylmethyl-5(R)-(2-(1,3-dithiolanyl))-2-oxazolidone was converted via the N-t-Boc oxazolidone (FAB-MS 388 (M⁺ + H, 10%) and 332 (M⁺ + H-C₄H₈, 100%)) and the N-t-Boc derivative of the title substance (FAB-MS 362 (M⁺ + H, 35%) to the title substance. ¹H NMR (CDCl₃, partial) δ 4.63 (d, 1H, J = 6.9 Hz). FAB-MS 262 (M⁺ + H, 100%).

Example 277

15 N-t-Butoxycarbonyl-4(S)-cyclohexylmethyl-2,2-dimethyl-5(R)-isopropoxycarbonyloxazolidine

A solution of Boc-norCSta isopropyl ester (15.4 g) and 400 mg p-toluenesulfonic acid in 180 ml 2,2-dimethoxypropane was stirred at 40 °C for 72 hours and diluted with 900 ml of ether. The resulting solution was washed with saturated aqueous NaHCO₃, dried and concentrated. The residue was chromatographed on 900 g silica eluted with 5% ethyl acetate in hexane giving 13.5 g of the title substance. FAB-MS 384 (M⁺ + H, 10%), 284 ((M⁺ + H-C₄H₈CO₂, 100%). ¹H NMR (CDCl₃, partial) δ 1.25 (d, 6H), 1.44 (s, 9H), 4.26 (m, 2H), 5.04 (m, 1H).

Example 278

25 N-t-Butoxycarbonyl-4(S)-cyclohexylmethyl-2,2-dimethyl-5(R)-pentafluoroethylcarbonyloxazolidine

To 26 g of iodoperfluoropropane was introduced a -15 °C solution of the substance of the preceding example (2 g) in 25 ml ether. The resulting solution was cooled to -78 °C and treated over 15 min with 20 ml of 1.3 M methyllithiumlithium bromide complex. After 1 hour 6 ml of saturated aqueous NH₄Cl was added and the mixture extracted with ether. The organic layers were combined and washed successively with saturated aqueous NaHCO₃, 1N HCl, saturated aq. NaHCl₃, brine, dried, and concentrated and the residue chromatographed on silica in ethyl acetate-hexane (a gradient beginning with 1% ethyl acetate) giving 785 mg of the title substance. ¹H NMR (DMSO-D₆, partial) δ 1.41 (s, 9H), 1.56 (s, 6H). ¹³C NMR (DMSO-D₆, partial) δ 93.57 (t, hydrated ketone carbonyl) 119.09 (qt, CF₂), 113.06 (tq, CF₃), 150 (s, CONH).

Example 279

40 N-t-Butoxycarbonyl-4(S)-cyclohexylmethyl-2,2-dimethyl-5(R)-1-(1,1,1,2,2-pentafluoro-1-hydroxypropyl)-oxazolidine

A solution of the compound of the preceding example (764 mg) in ethanol (9 ml) was treated at 25 °C with 65 mg sodium borohydride. After 2 hours the mixture was diluted with 50 ml ethyl acetate and the resulting solution stirred with 10 ml in HCl. The layers were separated and the organic layer washed with saturated aqueous NaHCO₃, brine, dried, and concentrated. The residue was chromatographed on silica eluted with an ethyl acetate-hexane gradient beginning with 1% ethyl acetate giving 521 mg of the major, faster moving component, a colorless solid. ¹H NMR (CDCl₃, partial) δ 1.46 (s, 9H), 1.52 (s, 3H), 1.62 (s, 3H), 3.07 (d, 1H), 4.14 (t, 1H). ¹³C NMR (CDCl₃) δ 151.2 (s), ea. 120.8 (qt, CF₃), ca. 113.1 (tq, CF₂), 95 (s), 80.4 (s), 76.4 (s), 68.61 (t), 57.5 (d), 34.58 (s), 32.14 (s), 28.36 (s), 26.30 (s), 26.21 (s), 25.89 (s). FAB-MS 446 (M⁺ + H, 15%), 390 (M⁺ + H-C₄H₈, 100%) 346 (M⁺ + H-C₄H₈CO₂, 75%).

Example 280

55 5(S)-Amino-6-cyclohexyl-4(R)-hydroxy-1,1,1,2,2-pentafluoro-3-hexanol

The product of the preceding Example (139 mg) was dissolved in 9 ml of 1:1:1 1N HCl-THF-acetic acid and the resulting solution was heated at 50 °C for 54 hours and stirred at 25 °C for 72 hours ether and water was added and the layers separated. The basic component was isolated by acid/base extraction using ethyl acetate giving 94 mg of residue which was chromatographed on silica eluted with a dichloromethane-

ethanol gradient beginning with 1% of the latter. 70 mg of the title substance was thus obtained, TLC R_f 0.13 in 18/2/1 $\text{CHCl}_3/\text{EtOH}/\text{HOAc}$.

Example 281

5

S-MeCys-nor-CSta N-methylamide Hydrochloride

685 mg Boc-S-methylcysteine and 729 mg nor-cSta N-methylamide were coupled according to General Procedure C and the product purified by chromatography on silica gel eluting with 1:4 ethyl acetate-hexanes, giving 850 mg of the protected dipeptide. This material was deprotected according to general
10 procedure-D and the residue washed with ether giving 499 mg of the title substance. FAB-MS 332 (100%, $M^+ + H$), ^1H NMR ($\text{DMSO}-d_6$, partial) δ 2.12 (s, 3H), 2.57 (d, 3H), 2.62 (dd, 1H), 2.95 (dd, 1H), 3.85 (d, 1H), 3.96 (m, 1H), 4.09 (m, 1H). By the same general sequence, using the appropriate Boc-amino acid and amine, the following compounds were prepared. As individually noted, trifluoroacetic acid could be
15 substituted for HCl-dioxane, and the free amine could be isolated by dissolution of the trifluoroacetic acid salt in ethyl acetate followed by extraction with aqueous base. Alternatively, the trifluoroacetic acid salt could be converted to the hydrochloride by dissolution in a slight excess of 9H dioxane-HCl at 0°C and evaporation.

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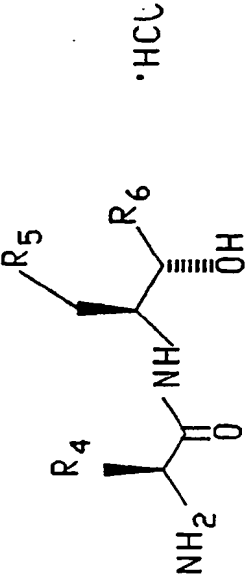
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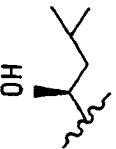
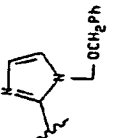
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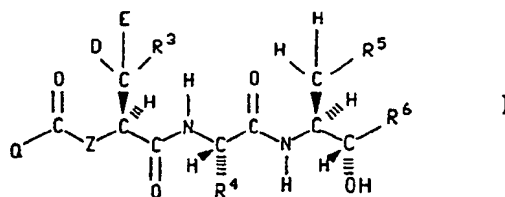
Example	R ₄	R ₅	R ₆	FAB-MS Base, M ⁺ + H (%)	¹ H NMR (partial), δ
282	CH ₂ SCH ₃	Cy		358 (100)	(D ₂ O) 2.07 (s, 3H), 2.65 (dd, 1H) 2.85 (dd, 1H), 4.09 (dd, 1H), 4.53 (m, 1H), 5.35 (d, 1H), 7.85 (d, 1H), 8.01 (d, 1H).
283*	CH ₂ SCH ₃	Cy			(D ₂ O) 0.87 (d, 3H), 0.93 (d, 3H), 2.19 (s, 3H), 2.99 (dd, 1H), 3.11 (dd, 1H), 3.38 (m, 1H), 3.51 (m, 1H), 4.19 (dd, 1H), 4.32 (m, 1H)

Example	R ₄	R ₃	R ₆	FAB-MS Base, M ⁺ + H (%)	¹ H NMR (partial), δ
284 ^b	iPr	Ph		337 (100)	(CDCl ₃) 0.33, 0.83, 0.85, and 0.92 (d, 3H ea), 1.88 (m, 1H), 2.18 (m, 1H), 4.52 (, 1H).
285	n-Pr	Cy	COOiPr		
286	iPr	Ph	COOiPr		
287	CH ₂ SCH ₃	Cy		461 (100)	(D ₂ O) 2.15 (s, 3H), 2.76 and 2.98 (dd, 1H ea), 4.14 (dd, 1H), 5.20 (d, 1H), 5.73 (m, 2H)
288	CH ₂ C=CH ₂	Cy	COOiPr		(DMSO) 1.18 (d, 6H), 3.83, 4.01, 4.23, and 4.84 (m, 1H ea), 5.15 (m, 2H), 5.6 (d, 1H), 5.7 (m, 1H)

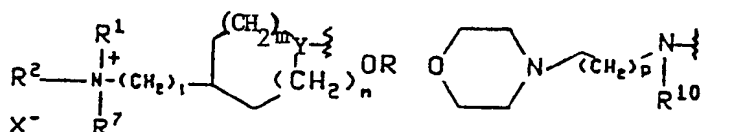
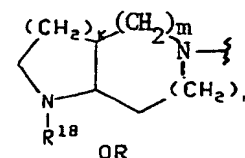
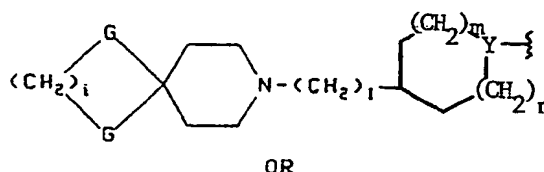
*a = Boc cleaved with TFA, and HCl salt formed with HCl-dioxane at 0°C.
 *b = Boc cleaved with TFA, free base isolated.

Claims

1. A compound of the formula



wherein Q is



with the proviso that R⁷ may be absent and that when R⁷ is absent the nitrogen does not carry a positive charge and X⁻ is absent;

x⁻ represents a pharmaceutically acceptable anion or shared anion;

l is 0, 1, 2 or 3;

k is 1, 2 or 3;

m and n are independently 0, 1 or 2;

each i is independently 2, 3 or 4;

each G is independently oxygen or sulfur;

Y is CH or N;

R¹ and R² are independently selected from hydrogen, C₁ to C₈ alkyl, amino-C₁ to C₈ alkyl, hydroxy-C₁ to C₈ alkyl, C₁ to C₆ alkoxy-C₂ to C₈ alkyl, C₁ to C₆ alkylamino-C₂ to C₈ alkyl, phenyl, naphthyl, pyridyl, imidazolyl, thiazolyl, di(C₁ to C₈alkyl)amino-C₂ to C₈ alkyl, or C₁ to C₈ alkoxycarbonyl-C₁ to C₈ alkyl; or R¹ and R² taken together with the nitrogen atom to which they are attached form a 4 to 8 membered ring containing 0, 1 or 2 atoms selected from the group consisting of oxygen, nitrogen and sulfur, the remaining atoms in the ring being carbon, said ring optionally containing one, two, or three double bonds, and said ring optionally containing one or two substituents selected from hydroxy and C₁ to C₆ alkyl, each hydroxy substituent, when present, being attached to a carbon in the ring and each C₁ to C₆ alkyl substituent, when present, being attached to a carbon or nitrogen in the ring;

R⁷ is C₁ to C₈ alkyl, phenyl-C₁ to C₈ alkyl, phenyl-C₁ to C₈ alkyl-C₁ to C₈ alkylamino;

p is 1 or 2;

R¹⁰ is hydrogen, C₁ to C₈ alkyl or phenyl-C₁ to C₈ alkyl;

Z is CH₂, O or NR¹³ wherein R¹³ is hydrogen or C₁ to C₅ alkyl;

D and E are independently selected from hydrogen and C₁ to C₃ alkyl, or D and E taken together with the carbon to which they are attached form a cyclopropyl, cyclobutyl or cyclopentyl ring;

R³ is phenyl, substituted phenyl, C₅ to C₇ cycloalkyl, C₅ to C₇ cycloalkylmethyl, 1-naphthyl, 2-naphthyl, substituted C₅ to C₇ cycloalkyl, phenylmethyl, substituted phenylmethyl, 2-thienyl, substituted 2-thienyl, 3-thienyl or substituted 3-thienyl, said substituted phenyl, substituted C₅ to C₇ cycloalkyl, substituted

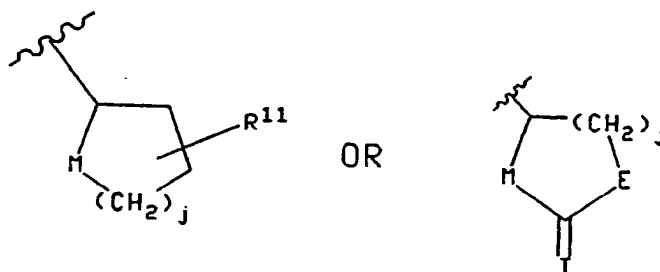
phenylmethyl, substituted 2-thienyl or substituted 3-thienyl being substituted with one or two groups selected from the group consisting of C₁ to C₅ alkoxy, C₁ to C₅ alkyl, halogen and hydroxy;

R⁴ is C₁ to C₈ alkyl, C₁ to C₈ substituted alkyl wherein the alkyl moiety is substituted with hydroxy or one to seven fluorine atoms; HCF₂S-C₁ to C₅ alkyl, 4-imidazolylmethyl, 4-thiazolylmethyl, C₂ to C₈ alkenyl-methyl, C₁ to C₈ alkyl-O-C₁ to C₈ alkyl, or C₁ to C₈ alkyl-S-C₁ to C₈ alkyl;

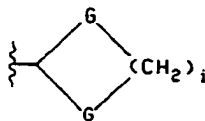
R⁵ is 2-thienyl, 3-thienyl, C₅ to C₇ cycloalkenyl, or 1,4-cyclohexadienyl, C₁ to C₈ alkyl, substituted C₁ to C₈ alkyl, C₁-C₈ alkoxy, phenyl or substituted phenyl, wherein said substituted C₁ to C₈ alkyl and said substituted phenyl are substituted with one or two substituents selected from the group consisting of C₁ to C₅ alkoxy, C₁ to C₅ alkyl, halogen, hydroxy and oxo, or said substituted C₁ to C₈ alkyl is substituted with one to seven fluorine atoms;

R⁶ is CO-C₁ to C₈ alkyl, COO-C₁ to C₁₀ alkyl, COCH₂-phenyl, COOCH₂-C₁ to C₈ substituted alkyl wherein the alkyl moiety is perfluorinated or substituted with 1 to 7 fluorine atoms; C₁ to C₈ alkyl-thiomethyl, 2-imidazolyl, 2-thiazolyl, 2-oxazolyl, wherein said 2-imidazolyl, 2-thiazolyl and 2-oxazolyl may optionally be substituted at one or two carbon atoms of the ring with one or two substituents independently selected from hydrogen, C₁ to C₈ alkyl, C₂ to C₅ alkenyl, halogen and C₁ to C₅ alkoxy carbonyl, and wherein said imidazolyl may additionally be substituted on one of the ring nitrogens with a substituent selected from C₁ to C₅ alkyl; phenyl, C₅ to C₇ cycloalkyl, CONR¹⁶R¹⁷ wherein R¹⁶ and R¹⁷ are independently selected from the group of radicals set forth in the definition of R¹ and R² above, except that R¹⁶ and R¹⁷ cannot, taken together with the nitrogen atom to which they are attached, form a ring, or CONHR⁸ wherein R⁸ is C₁ to C₈ alkyl or C₁ to C₈ alkyl substituted with 1 to 3 halogen atoms or with a 4-morpholino, thiazolyl or imidazolyl group, or substituted with a group selected from the group of radicals set forth in the definition of Q above;

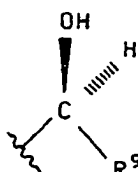
or R⁶ is a group of the formula



wherein j is 1 or 2; R¹¹ is hydrogen, C₁ to C₆ alkyl or CH₂OH; M is O, S, NR¹² wherein R¹² is hydrogen or C₁ to C₆ alkyl; T is O or S; E is O, S, C=CH₂, NR¹⁴ wherein R¹⁴ is hydrogen or C₁ to C₆ alkyl, or CHR¹⁵ wherein R¹⁵ is C₁ to C₆ alkyl; or R⁶ is a group of the formula



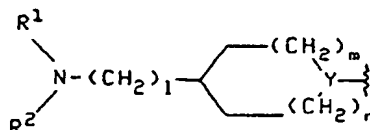
wherein each X is independently oxygen or sulfur and each i is independently 2, 3 or 4; or R⁶ is a group of the formula



wherein R⁹ is C₁ to C₁₃ alkyl, C₂ to C₈ alkenyl, phenyl-C₁ to C₈ alkyl, or substituted C₁ to C₈ alkyl

wherein the alkyl is perfluorinated or is substituted with hydroxy or 1 to 7 fluorine atoms;
and R¹⁸ is selected from the group of radicals set forth in the definition of R¹ and R² above, except that R¹⁸ can not be a member of a ring;
or a pharmaceutically acceptable salt thereof.

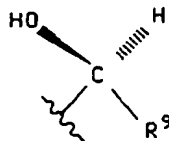
2. A compound according to claim 1, wherein Q is



Y is CH or N; m and n are each 1; Z is NH, O or CH₂; and l is 0 or 1.

3. A compound according to claim 1 or claim 2, wherein D and E are both hydrogen; R³ is phenyl, p-methoxyphenyl, benzyl, 1-naphthyl, cyclohexyl, 2-thienyl or 3-thienyl; R⁴ is C₁ to C₅ alkyl, C₁ to C₅ alkylthio-C₁ to C₃ alkyl, C₁ to C₅ alkoxy-C₁ to C₃ alkyl, C₂ to C₄ alkenylmethyl, 4-imidazolylmethyl or 4-thiazolylmethyl; R₅ is cyclohexyl or isopropyl; and R⁶ is -COO-C₁ to C₁₀ alkyl, -COO-C₁ to C₈ substituted alkyl wherein the alkyl is substituted with 1,2, or 3 fluorine atoms, or CONHR⁸ wherein R⁸ is C₁ to C₈ alkyl or C₁ to C₈ alkyl substituted with 1 to 3 fluorine atoms.

4. A compound according to claim 1 or claim 2, wherein D and E are both hydrogen; R³ is phenyl, p-methoxyphenyl, benzyl, 1-naphthyl, cyclohexyl, 2-thienyl or 3-thienyl; R⁴ is C₁ to C₅ alkyl, C₁ to C₅ alkylthio-C₁ to C₃ alkyl, C₁ to C₅ alkoxy-C₁ to C₃ alkyl, C₂ to C₄ alkenylmethyl, 4-imidazolylmethyl or 4-thiazolylmethyl; R₅ is cyclohexyl or isopropyl; and R⁶ is



R⁹ is C₁ to C₈ alkenyl, C₁ to C₁₃ cycloalkylalkyl, or C₁ to C₅ alkyl optionally substituted with 1 to 7 fluorine atoms.

5. A compound according to claim 2, said compound being selected from those wherein:

- D is hydrogen, E is hydrogen, R⁷ is methyl, R¹ is methyl, R² is methyl, m and n are 1, l is 0, Z is NH, Y is N, R³ is phenyl, R⁴ is methylthiomethyl, R⁵ is cyclohexyl, X is iodide and R⁶ is COO-isopropyl; or
- D is hydrogen, E is hydrogen, R⁷ is methyl, R¹ is methyl, R² is methyl, m and n are 1, l is 0, Z is CH₂, Y is N, R³ is phenyl, R⁴ is methylthiomethyl, R⁵ is cyclohexyl, X is iodide and R⁶ is COO-isopropyl; or
- D is hydrogen, E is hydrogen, R⁷ is absent, R¹ is ethyl, R² is methyl, m and n are 1, l is 0, Z is CH₂, Y is N, R³ is phenyl, R⁴ is methylthiomethyl, R⁵ is cyclohexyl, and R⁶ is COO-isopropyl; or
- D is hydrogen, E is hydrogen, R⁷ is absent, R¹ is methyl, R² is methyl, m and n are 1, l is 0, Z is CH₂, Y is N, R³ is phenyl, R⁴ is methylthiomethyl, R⁵ is cyclohexyl, and R⁶ is COO-(trans-2, trans-4-dimethylcyclopent-r-1-yl); or
- D is hydrogen, E is hydrogen, R⁷ is absent, R¹ is methyl, R² is methyl, m and n are 1, l is 0, Z is CH₂, Y is N, R³ is phenyl, R⁴ is methylthiomethyl, R⁵ is cyclohexyl, and R⁶ is COO-(trans-2, trans-5-dimethylcyclopent-r-1-yl); or
- D is hydrogen, E is hydrogen, R⁷ is absent, R¹ is methyl, R² is methyl, m and n are 1, l is 0, Z is NH, Y is CH, R³ is phenyl, R⁴ is methylthiomethyl, R⁵ is cyclohexyl, and R⁶ is COO-isopropyl; or
- D is hydrogen, E is hydrogen, R⁷ is absent, R¹ is methyl, R² is methyl, m and n are 1, l is 0, Z is NH, Y is N, R³ is cyclohexyl, R⁴ is methylthiomethyl, R⁵ is cyclohexyl, and R⁶ is COO-isopropyl; or
- D is hydrogen, E is hydrogen, R⁷ is absent, R¹ is methyl, R² is methyl, m and n are 1, l is 0, Z is

NH, Y is N, R³ is phenyl, R⁴ is methylthiomethyl, R⁵ is cyclohexyl, and R⁶ is COO-isopropyl; or
 i) D is hydrogen, E is hydrogen, R⁷ is absent, R¹ and R² taken together form a 4-methylpiperazine ring, m and n are 1, l is 0, Z is NH, Y is N, R³ is phenyl, R⁴ is methylthiomethyl, R⁵ is cyclohexyl, and R⁶ is COO-isopropyl; or

j) D is hydrogen, E is hydrogen, R⁷ is absent, R¹ and R² taken together form a pyrrolidine ring, m and n are 1, l is 0, Z is NH, Y is N, R³ is phenyl, R⁴ is methylthiomethyl, R⁵ is cyclohexyl, and R⁶ is COO-isopropyl; or

k) D is hydrogen, E is hydrogen, R⁷ is absent, R¹ is methyl, R² is methyl, m and n are 1, l is 0, Z is CH₂, Y is N, R³ is phenyl, R⁴ is methylthiomethyl, R⁵ is cyclohexyl, and R⁶ is COO-isopropyl; or

l) D is hydrogen, E is hydrogen, R⁷ is absent, R¹ is methyl, R² is methyl, m and n are 1, l is 0, Z is CH₂, Y is N, R³ is phenyl, R⁴ is methylthiomethyl, R⁵ is cyclohexyl, and R⁶ is COO-(3-pentyl); or

m) D is hydrogen, E is hydrogen, R⁷ is absent, R¹ is methyl, R² is methyl, m and n are 1, l is 0, Z is NH, Y is N, R³ is phenyl, R⁴ is methylthiomethyl, R⁵ is cyclohexyl, and R⁶ is COO-(3-pentyl); or

n) D is hydrogen, E is hydrogen, R⁷ is absent, R¹ is methyl, R² is methyl, m and n are 1, l is 0, Z is NH, Y is N, R³ is phenyl, R⁴ is methylthiomethyl, R⁵ is cyclohexyl, and R⁶ is COO-(2,2-dimethylcyclopentyl); or

o) D is hydrogen, E is hydrogen, R⁷ is absent, R¹ is methyl, R² is methyl, m and n are 1, l is 0, Z is NH, Y is N, R³ is phenyl, R⁴ is methylthiomethyl, R⁵ is cyclohexyl, and R⁶ is COO-(trans-2, trans-4-dimethylcyclopentane); or

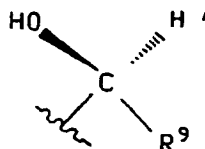
p) D is hydrogen, E is hydrogen, R⁷ is absent, R¹ is ethyl, R² is ethyl, m and n are 1, l is 0, Z is CH₂, Y is N, R³ is phenyl, R⁴ is methylthiomethyl, R⁵ is cyclohexyl, and R⁶ is COO-isopropyl; or

q) D is hydrogen, E is hydrogen, R⁷ is absent, R¹ is methyl, R² is methyl, m and n are 1, l is 0, Z is CH₂, Y is N, R³ is 2-thienyl, R⁴ is methylthiomethyl, R⁵ is cyclohexyl, and R⁶ is COO-isopropyl; or

r) D is hydrogen, E is hydrogen, R⁷ is absent, R¹ is hydrogen, R² is methyl, m and n are 1, l is 0, Z is CH₂, Y is N, R³ is phenyl, R⁴ is methylthiomethyl, R⁵ is cyclohexyl, and R⁶ is COO-isopropyl; or

s) D is hydrogen, E is hydrogen, R⁷ is absent, R¹ is methyl, R² is methyl, m and n are 1, l is 0, Z is CH₂, Y is N, R³ is phenyl, R⁴ is methylthiomethyl, R⁵ is cyclohexyl, and R⁶ is COO-(2,2-dimethylcyclopentyl).

6. A compound according to claim 2, said compound being selected from those wherein R⁶ is



and

a) D is hydrogen, E is hydrogen, R⁷ is absent, R¹ and R² taken together form a piperidine ring, m and n are 1, l is 0, Z is NH, Y is N, R³ is phenyl, R⁴ is methylthiomethyl, R⁵ is cyclohexyl, and R⁹ is isobutyl; or

b) D is hydrogen, E is hydrogen, R⁷ is absent, R¹ and R² taken together form a piperidine ring, m and n are 1, l is 0, Z is CH₂, Y is N, R³ is phenyl, R⁴ is methylthiomethyl, R⁵ is cyclohexyl, and R⁹ is isobutyl; or

c) D is hydrogen, E is hydrogen, R⁷ is absent, R¹ is methyl, R² is methyl, m and n are 1, l is 0, Z is CH₂, Y is N, R³ is 2-thienyl, R⁴ is methylthiomethyl, R⁵ is cyclohexyl, and R⁹ is isobutyl; or

d) D is hydrogen, E is hydrogen, R⁷ is absent, R¹ is hydrogen, R² is methyl, m and n are 1, l is 0, Z is CH₂, Y is N, R³ is 3-thienyl, R⁴ is methylthiomethyl, R⁵ is cyclohexyl, and R⁹ is isobutyl; or

e) D is hydrogen, E is hydrogen, R⁷ is absent, R¹ is methyl, R² is methyl, m and n are 1, l is 2, Z is CH₂, Y is N, R³ is phenyl, R⁴ is methylthiomethyl, R⁵ is cyclohexyl, and R⁹ is isobutyl; or

f) D is hydrogen, E is hydrogen, R⁷ is absent, R¹ is hydrogen, R² is methyl, m and n are 1, l is 1, Z is CH₂, Y is N, R³ is phenyl, R⁴ is methylthiomethyl, R⁵ is cyclohexyl, and R⁹ is isobutyl; or

g) D is hydrogen, E is hydrogen, R⁷ is absent, R¹ is methyl, R² is methyl, m and n are 1, l is 0, Z is CH₂, Y is N, R³ is phenyl, R⁴ is methylthiomethyl, R⁵ is cyclohexyl, and R⁹ is 4-pentenyl; or

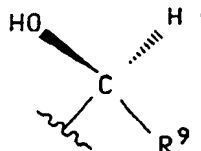
h) D is hydrogen, E is hydrogen, R⁷ is absent, R¹ is methyl, R² is methyl, m and n are 1, l is 0, Z is CH₂, Y is N, R³ is phenyl, R⁴ is methylthiomethyl, R⁵ is cyclohexyl, and R⁹ is 3-butenyl; or

i) D is hydrogen, E is hydrogen, R⁷ is absent, R¹ is methyl, R² is methyl, m and n are 1, l is 0, Z is

CH₂, Y is N, R³ is phenyl, R⁴ is methylthiomethyl, R⁵ is cyclohexyl, and R⁹ is cyclopentylmethyl.

7. A compound according to claim 16, said compound being selected from those wherein R⁶ is

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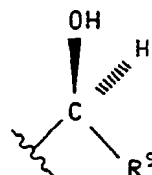
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and

- a) D is hydrogen, E is hydrogen, R⁷ is absent, R¹ is methyl, R² is methyl, m and n are 1, l is 0, Z is NH, Y is N, R³ is phenyl, R⁴ is methylthiomethyl, R⁵ is cyclohexyl, and R⁹ is isobutyl; or
 15 b) D is hydrogen, E is hydrogen, R⁷ is absent, R¹ is methyl, R² is methyl, m and n are 1, l is 0, Z is O, Y is N, R³ is phenyl, R⁴ is methylthiomethyl, R⁵ is cyclohexyl, and R⁹ is isobutyl; or
 c) D is hydrogen, E is hydrogen, R⁷ is absent, R¹ is methyl, R² is methyl, m and n are 1, l is 0, Z is CH₂, Y is N, R³ is phenyl, R⁴ is methylthiomethyl, R⁵ is cyclohexyl, and R⁹ is isobutyl; or
 20 d) D is hydrogen, E is hydrogen, R⁷ is absent, R¹ is methyl, R² is methyl, m and n are 1, l is 0, Z is NH, Y is N, R³ is p-methoxyphenyl, R⁴ is methylthiomethyl, R⁵ is cyclohexyl, and R⁹ is isobutyl.

8. A compound according to claim 2, with the proviso that when either R⁶ is

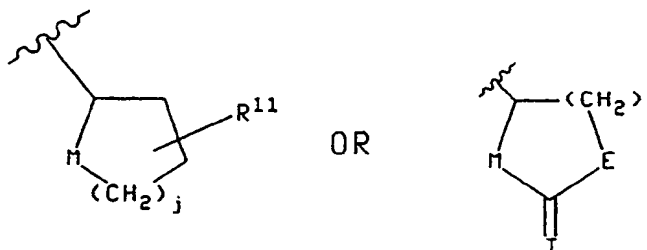
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wherein R⁹ is C₁ to C₈ alkyl, phenyl C₁ to C₈ alkyl or vinyl; or R⁶ is

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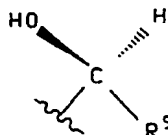
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wherein j is 1 or 2; R¹¹ is hydrogen, C₁ to C₆ alkyl or CH₂OH; M is O, S, NHR¹² wherein R¹² is hydrogen or C₁ to C₆ alkyl; T is O or S; and E is O, S, C=CH₂, NR¹⁴ wherein R¹⁴ is hydrogen or C₁ to C₆ alkyl, or CHR¹⁵ wherein R¹⁵ is C₁ to C₆ alkyl; then R⁷ is absent, Y is N, and neither R¹ nor R² is hydrogen or C₁-C₈ linear or branched alkyl.

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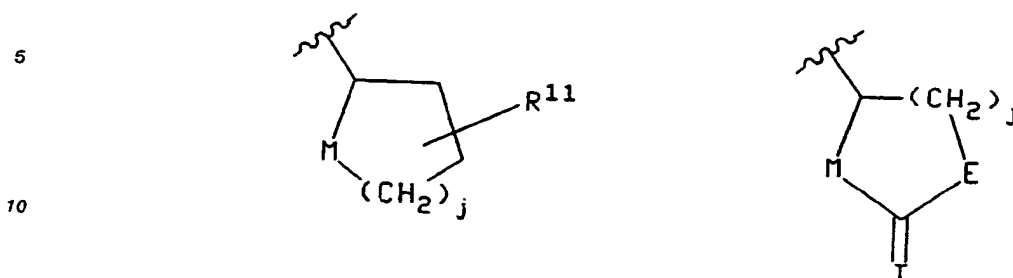
9. A compound according to claim 2, with the proviso that when either R⁶ is

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wherein R^9 is C_1 to C_8 alkyl, phenyl- C_1 to C_8 alkyl or vinyl, or R^6 is

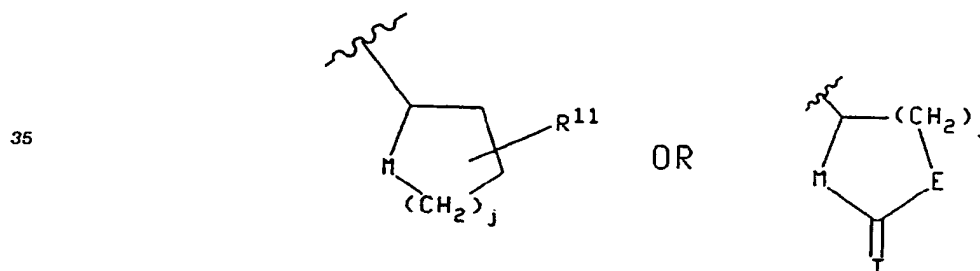


15 wherein j is 1 or 2; R^{11} is hydrogen, C_1 to C_6 alkyl or CH_2OH ; M is O, S or NR^{12} wherein R^{12} is hydrogen or C_1 to C_6 alkyl; T is O or S; and E is O, S, $C=CH_2$, NR^{14} wherein R^{14} is hydrogen or C_1 to C_6 alkyl, or CHR^{15} wherein R^{15} is C_1 to C_6 alkyl; then R^3 is 2-thienyl, substituted 2-thienyl, 3-thienyl, substituted 3-thienyl, said substituted 2- or 3-thienyl being substituted with one or two groups selected from C_1 to C_5 alkyl, C_1 to C_5 alkoxy, halogen and hydroxy.

20 10. A compound according to claim 2, with the proviso that when either R^6 is



30 wherein R^9 is C_1 to C_8 alkyl, phenyl- C_1 to C_8 alkyl or vinyl, or R^6 is



wherein j is 1 or 2; R^{11} is hydrogen, C_1 to C_6 alkyl or CH_2OH ; M is O, S or NR^{12} wherein R^{12} is hydrogen or C_1 to C_6 alkyl; T is O or S; E is O, S, $C=CH_2$, NR^{14} wherein R^{14} is hydrogen or C_1 to C_6 alkyl or CHR^{15} wherein R^{15} is C_1 to C_6 alkyl; then l is not equal to 0.

45 11. A pharmaceutical composition comprising a compound of the formula (I) as claimed in any one of the preceding claims and a pharmaceutically acceptable diluent or carrier.

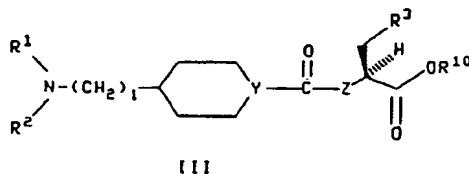
12. A composition as claimed in claim 11 which further comprises an additional antihypertensive agent.

50 13. A compound of the formula (I) as claimed in any one of claims 1 to 10 for use as a medicament.

14. The use of a compound of the formula (I) as claimed in any one of claims 1 to 10 for the manufacture of a medicament for treating hypertension, congestive heart failure, or glaucoma.

55 15. A compound of the formula

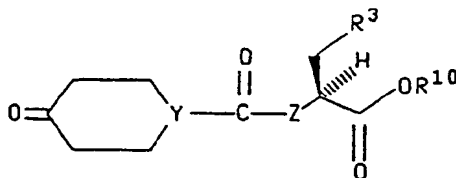
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10 wherein R¹ and R² are independently selected from hydrogen, C₁ to C₈ alkyl, di(C₁ to C₃ alkyl)amino-
C₂ to C₄ alkyl and nitrogen protecting groups or R¹ and R² taken together with the nitrogen to which
they are attached form a ring which is morpholine, 4-methylpiperazine, pyrrolidine, or piperidine; 1 is 0,
1, 2 or 3; Y is N or CH; Z is NH, O or CH₂; R³ is phenyl, p-methoxyphenyl, benzyl, 1-naphthyl,
cyclohexyl, 2-thienyl or 3- thienyl; and R¹⁰ is hydrogen, C₁ to C₃ alkyl or benzyl.

15 16. A compound of the formula

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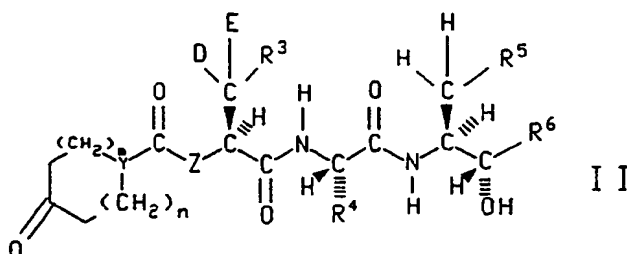


25 wherein Y is N or CH; Z is NH, O or CH₂; R³ is phenyl, p-methoxyphenyl, benzyl, 1-naphthyl,
cyclohexyl, 2-thienyl or 3- thienyl; and R¹⁰ is hydrogen, C₁ to C₃ alkyl or benzyl.

17. A compound of the formula

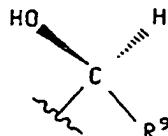
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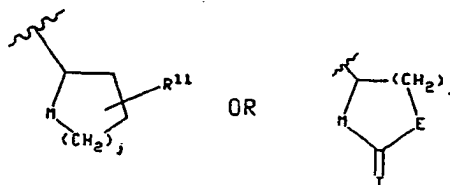


40 wherein m and n are independently 0 or 1; Y is CH or N; Z is CH₂, NH, O or NCH₃; D and E are
independently selected from hydrogen and C₁ to C₃ alkyl or D and E taken together with the carbon to
which they are attached form a cyclopropyl, cyclobutyl or cyclopentyl ring; R³ is phenyl, cyclohexyl, 1-
naphthyl, 2-thienyl, 3-thienyl, benzyl, or p-methoxybenzyl; R⁴ is C₁ to C₃ alkylthiomethyl, 4-imidazolyl-
methyl, C₁ to C₃ alkenyl-methyl, C₁ to C₃ alkoxy-methyl or C₂ to C₄ alkyl; R⁵ is cyclohexyl; R⁶ is
45 COO-C₁ to C₈ alkyl or CONR¹⁶R¹⁷ wherein R¹⁶ and R¹⁷ are independently selected from hydrogen and
C₁ to C₅ alkyl, with the proviso that when Y is N and Z is NH or NHCH₃, then R⁴ is C₁ to C₅ alkenyl-
methyl, and the pharmaceutically acceptable salts thereof.

18. A compound according to claim 2, wherein R⁷ is absent; R¹ and R² are independently selected from C₁
50 to C₇ linear or branched alkyl; 1 is 0; m and n are independently selected from 0 and 1; Y is nitrogen;
R³ is phenyl, substituted phenyl, C₅ to C₇ cycloalkyl, C₅ to C₇ cycloalkylmethyl, 1-naphthyl, 2-naphthyl,
substituted C₅ to C₇ cycloalkyl, phenylmethyl, substituted phenylmethyl, said substituted phenyl,
substituted C₅ to C₇ cycloalkyl and substituted phenylmethyl being substituted with one or two groups
selected from C₁ to C₅ alkoxy, C₁ to C₅ alkyl, halogen and hydroxy; R⁴ is C₁ to C₈ alkyl optionally
55 substituted with hydroxy; 4-imidazolylmethyl, 4-thiazolylmethyl, C₂ to C₈ alkenyl-methyl, C₁ to C₈ alkyl-
O-C₁ to C₈ alkyl, C₁ to C₈ alkyl-S-C₁ to C₈ alkyl; R⁵ is C₁ to C₆ linear or branched alkyl, C₄ to C₇
cycloalkyl-methyl or benzyl; R⁶ is



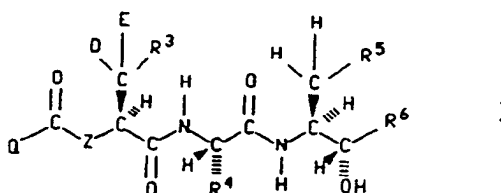
wherein R^9 is C_1 to C_8 alkyl, phenyl- C_1 to C_8 alkyl or vinyl, or R_6 is



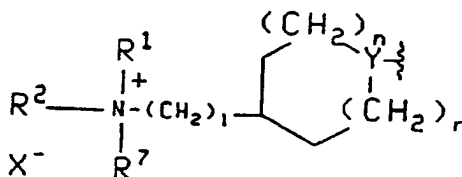
wherein j is 1 or 2; R^{11} is hydrogen, C_1 to C_6 alkyl or CH_2OH ; M is O, S or NR^{12} wherein R^{12} is hydrogen or C_1 to C_6 alkyl; T is O or S; E is O, S, $C=CH_2$, NR^{14} wherein R^{14} is hydrogen or C_1 to C_6 alkyl; or CHR^{13} wherein R^{13} is C_1 to C_6 alkyl.

Claims for the following Contracting States: ES

1. A process for preparing a compound of the formula



wherein Q is



with the proviso that R^7 may be absent and that when R^7 is absent the nitrogen does not carry a positive charge and X^- is absent;

X^- represents a pharmaceutically acceptable anion or shared anion;

l is 0, 1, 2 or 3;

k is 1, 2 or 3;

m and n are independently 0, 1 or 2;

each i is independently 2, 3 or 4;

each G is independently oxygen or sulfur;

Y is CH or N;

R^1 and R^2 are independently selected from hydrogen, C_1 to C_8 alkyl, amino- C_1 to C_8 alkyl, hydroxy- C_1 to C_8 alkyl, C_1 to C_6 alkoxy- C_2 to C_8 alkyl, C_1 to C_6 alkylamino- C_2 to C_8 alkyl, phenyl, naphthyl, pyridyl, imidazolyl, thiazolyl, di(C_1 to C_8 alkyl)amino- C_2 to C_8 alkyl, or C_1 to C_8 alkoxycarbonyl- C_1 to C_8 alkyl; or R^1 and R^2 taken together with the nitrogen atom to which they are attached form a 4 to 8

membered ring containing 0, 1 or 2 atoms selected from the group consisting of oxygen, nitrogen and sulfur, the remaining atoms in the ring being carbon, said ring optionally containing one, two, or three double bonds, and said ring optionally containing one or two substituents selected from hydroxy and C₁ to C₆ alkyl, each hydroxy substituent, when present, being attached to a carbon in the ring and each C₁ to C₆ alkyl substituent, when present, being attached to a carbon or nitrogen in the ring;

R⁷ is C₁ to C₈ alkyl, phenyl-C₁ to C₈ alkyl, phenyl-C₁ to C₈ alkyl-C₁ to C₈ alkylamino;

p is 1 or 2;

R¹⁰ is hydrogen, C₁ to C₈ alkyl or phenyl-C₁ to C₈ alkyl;

Z is CH₂, O or NR¹³ wherein R¹³ is hydrogen or C₁ to C₅ alkyl;

D and E are independently selected from hydrogen and C₁ to C₃ alkyl, or D and E taken together with the carbon to which they are attached form a cyclopropyl, cyclobutyl or cyclopentyl ring;

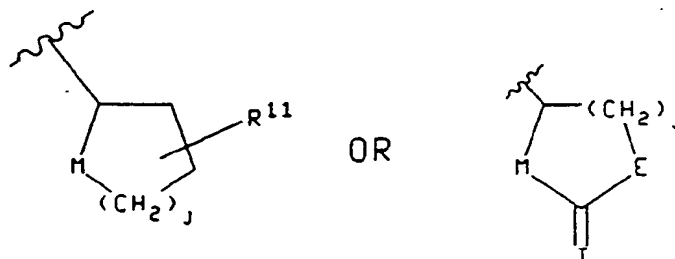
R³ is phenyl, substituted phenyl, C₅ to C₇ cycloalkyl, C₅ to C₇ cycloalkylmethyl, 1-naphthyl, 2-naphthyl, substituted C₅ to C₇ cycloalkyl, phenylmethyl, substituted phenylmethyl, 2-thienyl, substituted 2-thienyl, 3-thienyl or substituted 3-thienyl, said substituted phenyl, substituted C₅ to C₇ cycloalkyl, substituted phenylmethyl, substituted 2-thienyl or substituted 3-thienyl being substituted with one or two groups selected from the group consisting of C₁ to C₅ alkoxy, C₁ to C₅ alkyl, halogen and hydroxy;

R⁴ is C₁ to C₈ alkyl, C₁ to C₈ substituted alkyl wherein the alkyl moiety is substituted with hydroxy or one to seven fluorine atoms; HCF₂S-C₁ to C₅ alkyl, 4-imidazolylmethyl, 4-thiazolylmethyl, C₂ to C₈ alkenyl-methyl, C₁ to C₈ alkyl-O-C₁ to C₈ alkyl, or C₁ to C₈ alkyl-S-C₁ to C₈ alkyl;

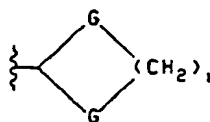
R⁵ is 2-thienyl, 3-thienyl, C₅ to C₇ cycloalkenyl, or 1,4-cyclohexadienyl, C₁ to C₈ alkyl, substituted C₁ to C₈ alkyl, C₁-C₈ alkoxy, phenyl or substituted phenyl, wherein said substituted C₁ to C₈ alkyl and said substituted phenyl are substituted with one or two substituents selected from the group consisting of C₁ to C₅ alkoxy, C₁ to C₅ alkyl, halogen, hydroxy and oxo, or said substituted C₁ to C₈ alkyl is substituted with one to seven fluorine atoms;

R⁶ is CO-C₁ to C₈ alkyl, COO-C₁ to C₁₀ alkyl, COCH₂-phenyl, COOCH₂-C₁ to C₈ substituted alkyl wherein the alkyl moiety is perfluorinated or substituted with 1 to 7 fluorine atoms; C₁ to C₈ alkyl-thiomethyl, 2-imidazolyl, 2-thiazolyl, 2-oxazolyl, wherein said 2-imidazolyl, 2-thiazolyl and 2-oxazolyl may optionally be substituted at one or two carbon atoms of the ring with one or two substituents independently selected from hydrogen, C₁ to C₈ alkyl, C₂ to C₅ alkenyl, halogen and C₁ to C₅ alkoxy carbonyl, and wherein said imidazolyl may additionally be substituted on one of the ring nitrogens with a substituent selected from C₁ to C₅ alkyl; phenyl, C₅ to C₇ cycloalkyl, CONR¹⁶R¹⁷ wherein R¹⁶ and R¹⁷ are independently selected from the group of radicals set forth in the definition of R¹ and R² above, except that R¹⁶ and R¹⁷ cannot, taken together with the nitrogen atom to which they are attached, form a ring, or CONHR⁸ wherein R⁸ is C₁ to C₈ alkyl or C₁ to C₈ alkyl substituted with 1 to 3 halogen atoms or with a 4-morpholino, thiazolyl or imidazolyl group, or substituted with a group selected from the group of radicals set forth in the definition of Q above;

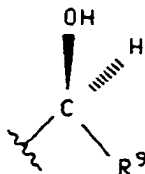
or R⁶ is a group of the formula



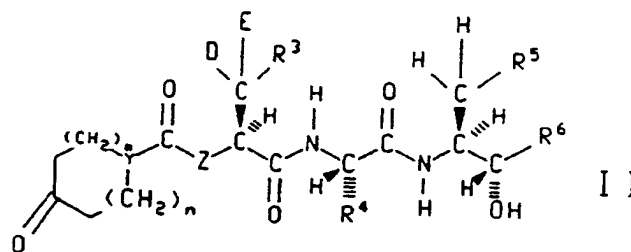
wherein j is 1 or 2; R¹¹ is hydrogen, C₁ to C₆ alkyl or CH₂OH; M is O, S, NR¹² wherein R¹² is hydrogen or C₁ to C₆ alkyl; T is O or S; E is O, S, C=CH₂, NR¹⁴ wherein R¹⁴ is hydrogen or C₁ to C₆ alkyl, or CHR¹⁵ wherein R¹⁵ is C₁ to C₆ alkyl; or R⁶ is a group of the formula



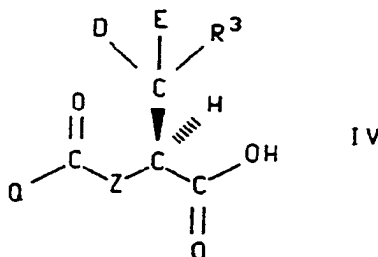
wherein each X is independently oxygen or sulfur and each i is independently 2, 3 or 4;
or R⁶ is a group of the formula



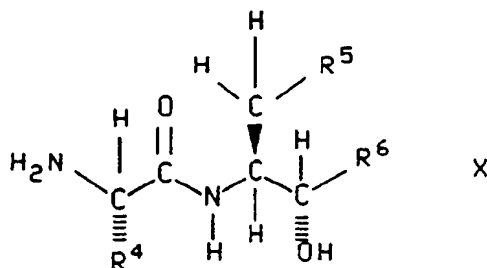
wherein R⁹ is C₁ to C₁₃ alkyl, C₂ to C₈ alkenyl, phenyl-C₁ to C₈ alkyl, or substituted C₁ to C₈ alkyl wherein the alkyl is perfluorinated or is substituted with hydroxy or 1 to 7 fluorine atoms;
and R¹⁸ is selected from the group of radicals set forth in the definition of R¹ and R² above, except that R¹⁸ can not be a member of a ring;
or a pharmaceutically acceptable salt thereof,
Comprising reacting a compound of the formula



- wherein Y, Z, D, E, R³, R⁴, R⁵, R⁶, m and n are as defined above, with (a) an amine of the formula R¹R²NH wherein R¹ and R² are defined as above, in the presence of a suitable reducing agent, or (b) the hydrochloride salt of an amine of the formula R¹R²NH, wherein R¹ and R² are defined as above; and optionally converting the product of such reaction to a pharmaceutically acceptable salt thereof.
2. A process for preparing a compound of the formula or a pharmaceutically acceptable salt thereof, comprising coupling a compound of the formula

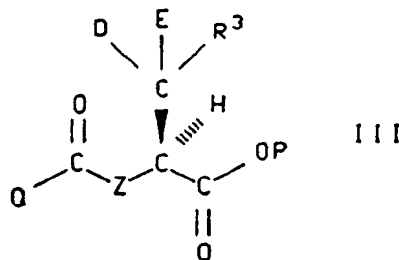


wherein Q, Z, D, E and R³ are defined as above, with a compound of the formula



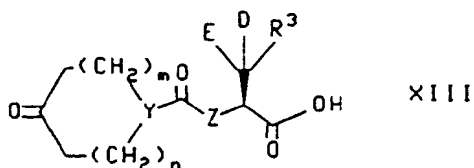
wherein R^4 , R^5 and R^6 are defined as above.

3. A process according to claim 2, wherein said compound of the formula IV is obtained by removing the protecting group (P) from a compound of the formula

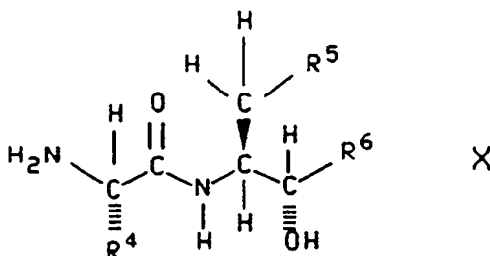


wherein Q, Z, D, E and R^3 are defined as in claim 2 and P is a protecting group.

4. A process according to claim 1, wherein said compound of formula II is obtained by coupling a compound of the formula



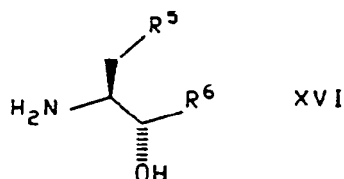
wherein Y, Z, E, D, R^3 , m and n are defined as in claim 1, with a compound of the formula



wherein R^4 , R^5 and R^6 are defined as in claim 1.

5. A process according to claim 1, wherein said compound of the formula II is obtained by coupling a compound of the formula

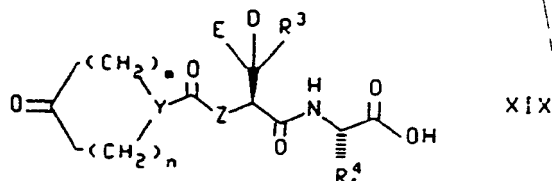
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wherein R⁵ and R⁶ are defined as in claim 1, with a compound of the formula

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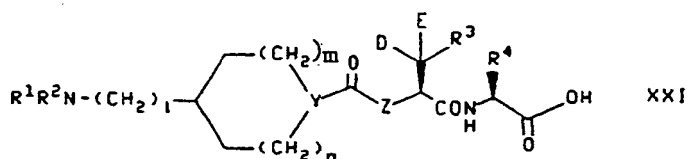
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wherein Y, Z, E, D, R³, R⁴, m and n are defined as in claim 1.

6. A process for preparing a compound of the formula I, as depicted and defined in claim 1, comprising coupling a compound of the formula XVI, as depicted and described in claim V, with a compound of the formula

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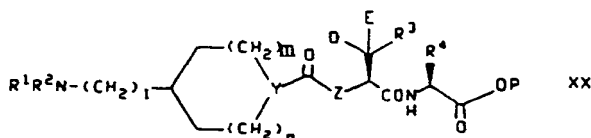


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wherein R¹, R², R³, R⁴, Y, Z, D, E, m and n are defined as in claim 1.

7. A process according to claim 6, wherein said compound of formula XXI is obtained by removing the protecting group (P) from a compound of the formula

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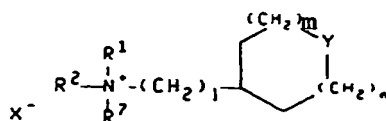


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wherein R¹, R², Y, Z, D, E, R³, R⁴, m and n are defined as in claim 1 and P is a protecting group.

8. A process according to claim 2, wherein said compounds of the formulae I and IV are compounds wherein Q is a radical of the formula J said radical having the formula

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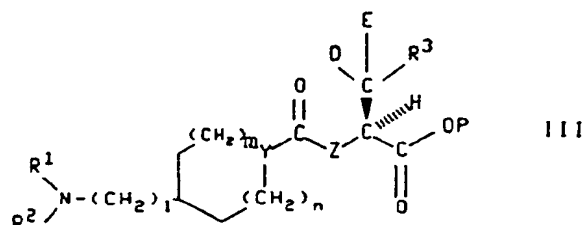
wherein R¹, R², R⁷, l, m and n are defined as in claim 2.

9. A process according to claim 3, wherein said compounds of the formulae I, IV and III are compounds wherein Q is a radical of the formula J, as defined in claim 8.

10. A process for preparing a compound of the formula

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wherein R^1 , R^2 , R^3 , Z, D, E, and I are defined as in claim 1, Y is N, each m and n is 1 and P is a protecting group, comprising reacting a compound of the formula

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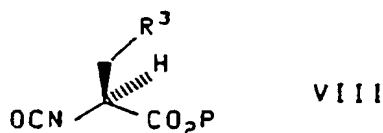


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wherein R^1 , R^2 and I are defined as in claim 1, with:

a) a compound of the formula

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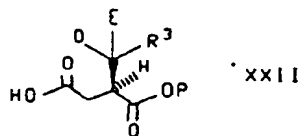
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wherein R^3 is defined as in claim 1 and P is a protecting group; or

b) a compound of the formula AA-OP, wherein AA is an appropriate alpha amino acid and P is a protecting group, in the presence of carbonyldiimidazole or another phosgene equivalent useful in urea formation; or

c) a compound of the formula

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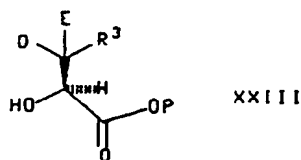
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wherein D, E, and R^3 are defined as in claim 1 and P is a protecting group, in the presence of a suitable coupling agent; or

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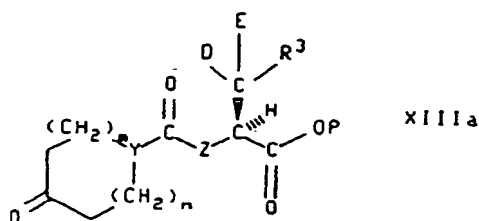
d) a compound of the formula

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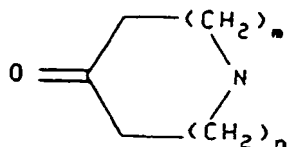


wherein D, E, and R³ are defined as in claim 1 and P is a protecting group, in the presence of carbonyldiimidazole or another phosgene equivalent useful in carbamate formation.

11. A process for making a compound of the formula

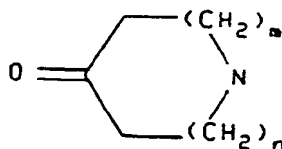


wherein Y is N, Z is CH₂, P is a protecting group and m, n, D, E and R³ are defined as in claim 1, comprising reacting a compound of the formula



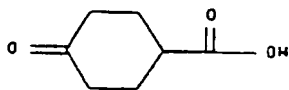
wherein m and n are defined as in claim 1, with a compound of the formula XXII, as depicted and defined in claim 10.

12. A process for preparing a compound of the formula XIIIa, as depicted in claim 11 and wherein Y is N, Z is O, P is a protecting group and m, n, D, E and R³ are defined as in claim 1, comprising reacting a compound of the formula



wherein m and n are defined as in claim 1, with a compound of the formula XXIII, as depicted and defined in claim 10.

13. A process for preparing a compound of the formula XIIIa, as depicted in claim 11 and wherein Y is CH, Z is N or O, P is a protecting group, each of m and n is 1, and D, E and R³ are defined as in claim 1, comprising coupling a compound of the formula



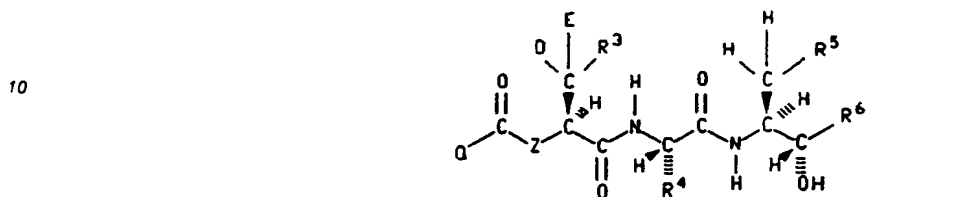
with:

- a) compound of the formula XXIII, as depicted and defined in claim 10 (when the desired compound of formula XIIIa is a compound wherein Z is O); or
- b) a compound of the formula AA-OP, wherein AA is an appropriate alpha amino acid and P is a

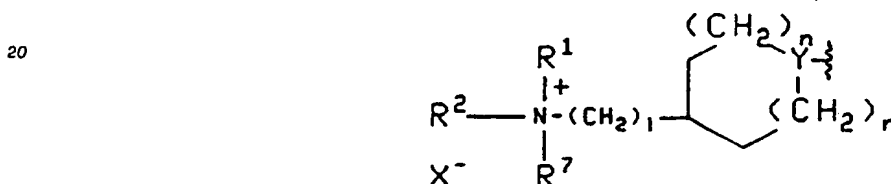
protecting group (when the desired compound of formula XIIIa is a compound wherein Z is NH).

Claims for the following Contracting State: GR

1. A process for preparing a compound of the formula



wherein Q is



with the proviso that R⁷ may be absent and that when R⁷ is absent the nitrogen does not carry a positive charge and X⁻ is absent;

X⁻ represents a pharmaceutically acceptable anion or shared anion;

l is O, 1, 2 or 3;

k is 1, 2 or 3;

m and n are independently 0, 1 or 2;

each i is independently 2, 3 or 4;

each G is independently oxygen or sulfur;

Y is CH or N;

R¹ and R² are independently selected from hydrogen, C₁ to C₈ alkyl, amino-C₁ to C₈ alkyl, hydroxy-C₁ to C₈ alkyl, C₁ to C₆ alkoxy-C₂ to C₈ alkyl, C₁ to C₆ alkylamino-C₂ to C₈ alkyl, phenyl, naphthyl, pyridyl, imidazolyl, thiazolyl, di(C₁ to C₈ alkyl)amino-C₂ to C₈ alkyl, or C₁ to C₈ alkoxy-carbonyl-C₁ to C₈ alkyl; or R¹ and R² taken together with the nitrogen atom to which they are attached form a 4 to 8 membered ring containing 0, 1 or 2 atoms selected from the group consisting of oxygen, nitrogen and sulfur, the remaining atoms in the ring being carbon, said ring optionally containing one, two, or three double bonds, and said ring optionally containing one or two substituents selected from hydroxy and C₁ to C₆ alkyl, each hydroxy substituent, when present, being attached to a carbon in the ring and each C₁ to C₆ alkyl substituent, when present, being attached to a carbon or nitrogen in the ring;

R⁷ is C₁ to C₈ alkyl, phenyl-C₁ to C₈ alkyl, phenyl-C₁ to C₈ alkylamino;

p is 1 or 2;

R¹⁰ is hydrogen, C₁ to C₈ alkyl or phenyl-C₁ to C₈ alkyl;

Z is CH₂, O or NR¹³ wherein R¹³ is hydrogen or C₁ to C₅ alkyl;

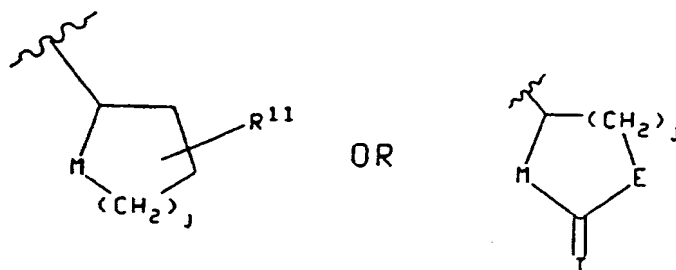
D and E are independently selected from hydrogen and C₁ to C₃ alkyl, or D and E taken together with the carbon to which they are attached form a cyclopropyl, cyclobutyl or cyclopentyl ring;

R³ is phenyl, substituted phenyl, C₅ to C₇ cycloalkyl, C₅ to C₇ cycloalkylmethyl, 1-naphthyl, 2-naphthyl, substituted C₅ to C₇ cycloalkyl, phenylmethyl, substituted phenylmethyl, 2-thienyl, substituted 2-thienyl, 3-thienyl or substituted 3-thienyl, said substituted phenyl, substituted C₅ to C₇ cycloalkyl, substituted phenylmethyl, substituted 2-thienyl or substituted 3-thienyl being substituted with one or two groups selected from the group consisting of C₁ to C₅ alkoxy, C₁ to C₅ alkyl, halogen and hydroxy;

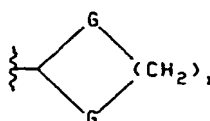
R⁴ is C₁ to C₈ alkyl, C₁ to C₈ substituted alkyl wherein the alkyl moiety is substituted with hydroxy or one to seven fluorine atoms; HCF₂S-C₁ to C₅ alkyl, 4-imidazolylmethyl, 4-thiazolylmethyl, C₂ to C₈ alkenyl-methyl, C₁ to C₈ alkyl-O-C₁ to C₈ alkyl, or C₁ to C₈ alkyl-S-C₁ to C₈ alkyl;

R⁵ is 2-thienyl, 3-thienyl, C₅ to C₇ cycloalkenyl, or 1,4-cyclohexadienyl, C₁ to C₈ alkyl, substituted C₁ to C₈ alkyl, C₁-C₈ alkoxy, phenyl or substituted phenyl, wherein said substituted C₁ to C₈ alkyl and said substituted phenyl are substituted with one or two substituents selected from the group consisting of C₁ to C₅ alkoxy, C₁ to C₅ alkyl, halogen, hydroxy and oxo, or said substituted C₁ to C₈ alkyl is substituted with one to seven fluorine atoms;

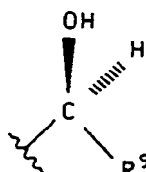
R⁶ is CO-C₁ to C₈ alkyl, COO-C₁ to C₁₀ alkyl, COCH₂-phenyl, COOCH₂-C₁ to C₈ substituted alkyl wherein the alkyl moiety is perfluorinated or substituted with 1 to 7 fluorine atoms; C₁ to C₈ alkyl-thiomethyl, 2-imidazolyl, 2-thiazolyl, 2-oxazolyl, wherein said 2-imidazolyl, 2-thiazolyl and 2-oxazolyl may optionally be substituted at one or two carbon atoms of the ring with one or two substituents independently selected from hydrogen, C₁ to C₈ alkyl, C₂ to C₅ alkenyl, halogen and C₁ to C₅ alkoxy carbonyl, and wherein said imidazolyl may additionally be substituted on one of the ring nitrogens with a substituent selected from C₁ to C₅ alkyl; phenyl, C₅ to C₇ cycloalkyl, CONR¹⁶R¹⁷ wherein R¹⁶ and R¹⁷ are independently selected from the group of radicals set forth in the definition of R¹ and R² above, except that R¹⁶ and R¹⁷ cannot, taken together with the nitrogen atom to which they are attached, form a ring, or CONHR⁸ wherein R⁸ is C₁ to C₈ alkyl or C₁ to C₈ alkyl substituted with 1 to 3 halogen atoms or with a 4-morpholino, thiazolyl or imidazolyl group, or substituted with a group selected from the group of radicals set forth in the definition of Q above; or R⁶ is a group of the formula



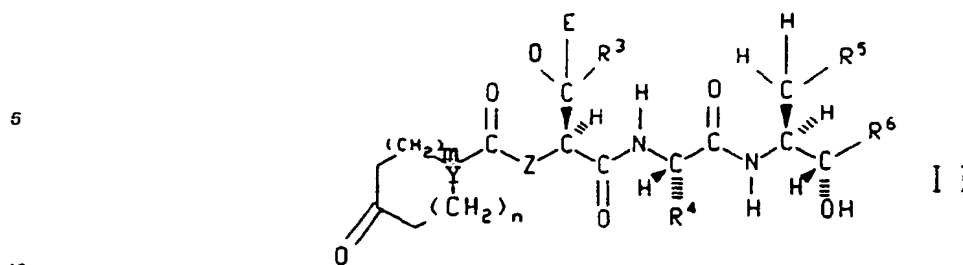
wherein j is 1 or 2; R¹¹ is hydrogen, C₁ to C₆ alkyl or CH₂OH; M is O, S, NR¹² wherein R¹² is hydrogen or C₁ to C₆ alkyl; T is O or S; E is O, S, C=CH₂, NR¹⁴ wherein R¹⁴ is hydrogen or C₁ to C₆ alkyl, or CHR¹⁵ wherein R¹⁵ is C₁ to C₆ alkyl; or R⁶ is a group of the formula



wherein each X is independently oxygen or sulfur and each i is independently 2, 3 or 4; or R⁶ is a group of the formula

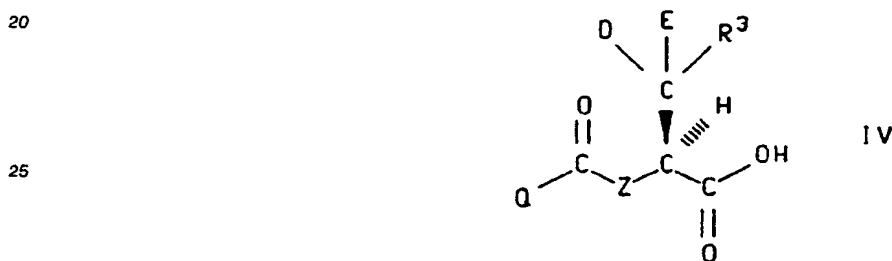


wherein R⁹ is C₁ to C₁₃ alkyl, C₂ to C₈ alkenyl, phenyl-C₁ to C₈ alkyl, or substituted C₁ to C₈ alkyl wherein the alkyl is perfluorinated or is substituted with hydroxy or 1 to 7 fluorine atoms; and R¹⁸ is selected from the group of radicals set forth in the definition of R¹ and R² above, except that R¹⁸ can not be a member of a ring; or a pharmaceutically acceptable salt thereof, Comprising reacting a compound of the formula

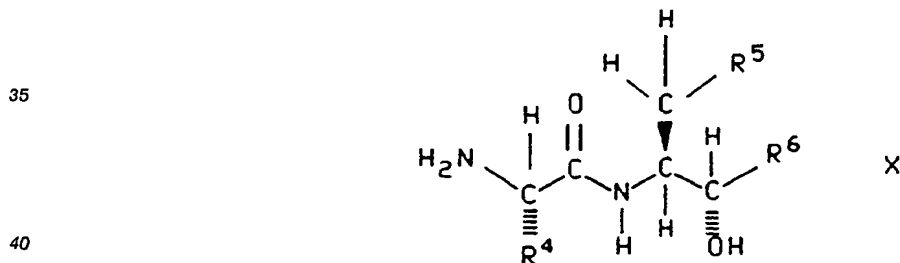


wherein Y, Z, D, E, R³, R⁴, R⁵, R⁶, m and n are as defined above, with (a) an amine of the formula R¹R²NH wherein R¹ and R² are defined as above, in the presence of a suitable reducing agent, or (b) the hydrochloride salt of an amine of the formula R¹R²NH, wherein R¹ and R² are defined as above; and optionally converting the product of such reaction to a pharmaceutically acceptable salt thereof.

2. A process for preparing a compound of the formula or a pharmaceutically acceptable salt thereof, comprising coupling a compound of the formula

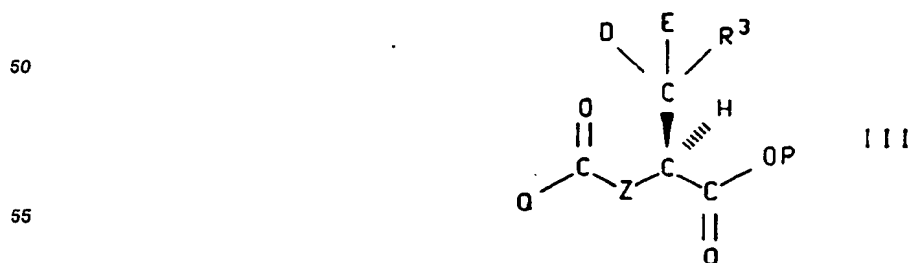


wherein Q, Z, D, E and R³ are defined as above, with a compound of the formula



wherein R⁴, R⁵ and R⁶ are defined as above.

3. A process according to claim 2, wherein said compound of the formula IV is obtained by removing the protecting group (P) from a compound of the formula

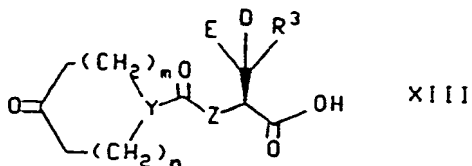


wherein Q, Z, D, E and R³ are defined as in claim 2 and P is a protecting group.

4. A process according to claim 1, wherein said compound of formula II is obtained by coupling a compound of the formula

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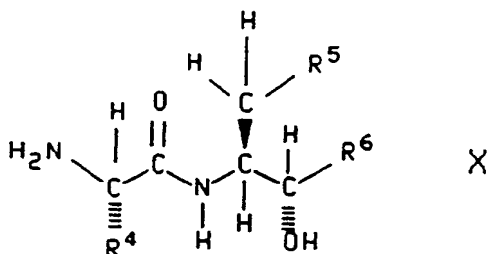
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wherein Y, Z, E, D, R³, m and n are defined as in claim 1, with a compound of the formula

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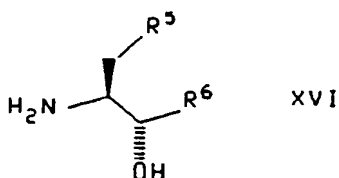
25

wherein R⁴, R⁵ and R⁶ are defined as in claim 1.

5. A process according to claim 1, wherein said compound of the formula II is obtained by coupling a compound of the formula

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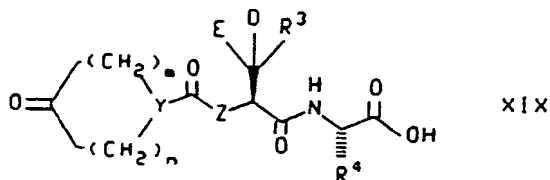
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wherein R⁵ and R⁶ are defined as in claim 1, with a compound of the formula

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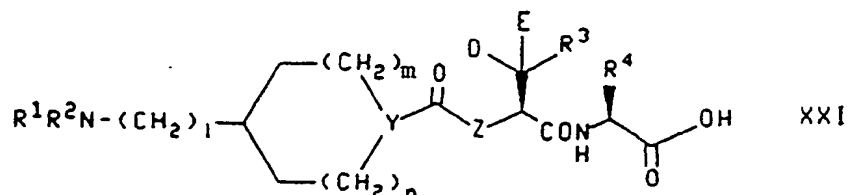


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wherein Y, Z, E, D, R³, R⁴, m and n are defined as in claim 1.

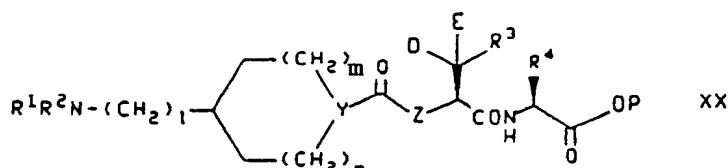
6. A process for preparing a compound of the formula I, as depicted and defined in claim 1, comprising coupling a compound of the formula XVI, as depicted and described in claim V, with a compound of the formula

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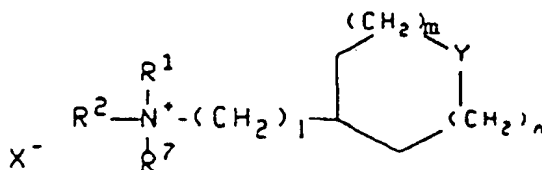
10 wherein R^1 , R^2 , R^3 , R^4 , Y , Z , D , E , m and n are defined as in claim 1.

7. A process according to claim 6, wherein said compound of formula XXI is obtained by removing the protecting group (P) from a compound of the formula



20 wherein R^1 , R^2 , Y , Z , D , E , R^3 , R^4 , m and n are defined as in claim 1 and P is a protecting group.

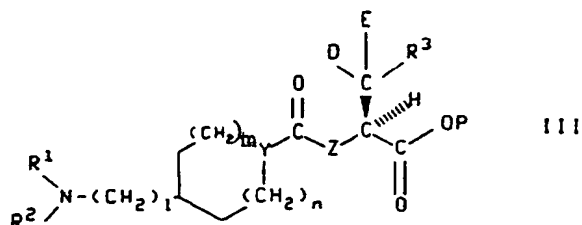
- 25 8. A process according to claim 2, wherein said compounds of the formulae I and IV are compounds wherein Q is a radical of the formula J said radical having the formula



wherein R^1 , R^2 , R^7 , l , m and n are defined as in claim 2.

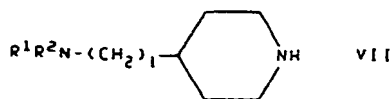
9. A process according to claim 3, wherein said compounds of the formulae I, IV and III are compounds wherein Q is a radical of the formula J, as defined in claim 8.

10. A process for preparing a compound of the formula



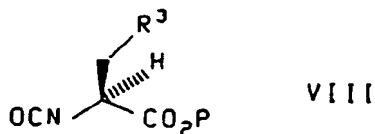
50 wherein R^1 , R^2 , R^3 , Z , D , E , and l are defined as in claim 1, Y is N, each m and n is 1 and P is a protecting group, comprising reacting a compound of the formula

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wherein R^1 , R^2 and l are defined as in claim 1, with:

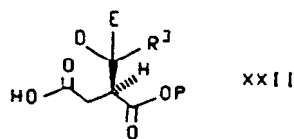
a) a compound of the formula



wherein R^3 is defined as in claim 1 and P is a protecting group; or

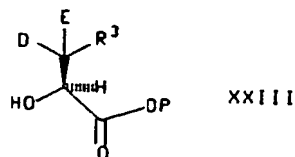
b) a compound of the formula AA-OP, wherein AA is an appropriate alpha amino acid and P is a protecting group, in the presence of carbonyldiimidazole or another phosgene equivalent useful in urea formation; or

c) a compound of the formula



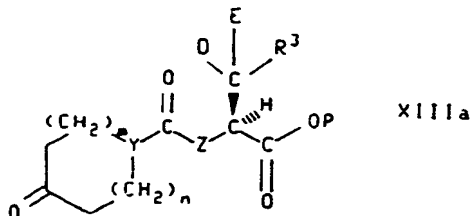
wherein D, E, and R^3 are defined as in claim 1 and P is a protecting group, in the presence of a suitable coupling agent; or

d) a compound of the formula

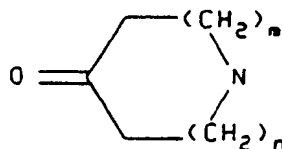


wherein D, E, and R^3 are defined as in claim 1 and P is a protecting group, in the presence of carbonyldiimidazole or another phosgene equivalent useful in carbamate formation.

11. A process for making a compound of the formula

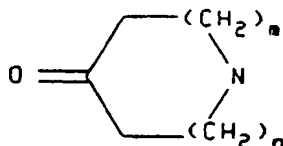


wherein Y is N, Z is CH_2 , P is a protecting group and m, n, D, E and R^3 are defined as in claim 1, comprising reacting a compound of the formula



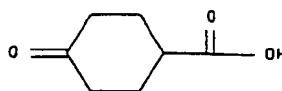
wherein m and n are defined as in claim 1, with a compound of the formula XXII, as depicted and defined in claim 10.

12. A process for preparing a compound of the formula XIIIa, as depicted in claim 11 and wherein Y is N, Z is O, P is a protecting group and m, n, D, E and R³ are defined as in claim 1, comprising reacting a compound of the formula



wherein m and n are defined as in claim 1, with a compound of the formula XXIII, as depicted and defined in claim 10.

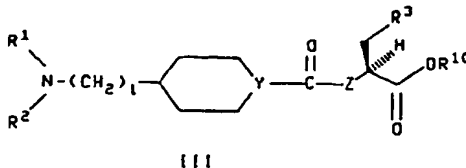
13. A process for preparing a compound of the formula XIIIa, as depicted in claim 11 and wherein Y is CH, Z is N or O, P is a protecting group, each of m and n is 1, and D, E and R³ are defined as in claim 1, comprising coupling a compound of the formula



with:

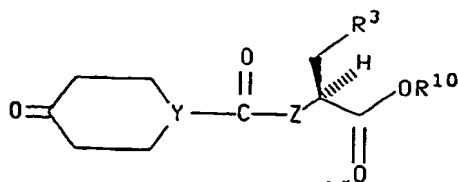
- compound of the formula XXIII, as depicted and defined in claim 10 (when the desired compound of formula XIIIa is a compound wherein Z is O); or
- a compound of the formula AA-OP, wherein AA is an appropriate alpha amino acid and P is a protecting group (when the desired compound of formula XIIIa is a compound wherein Z is NH).

14. A compound of the formula



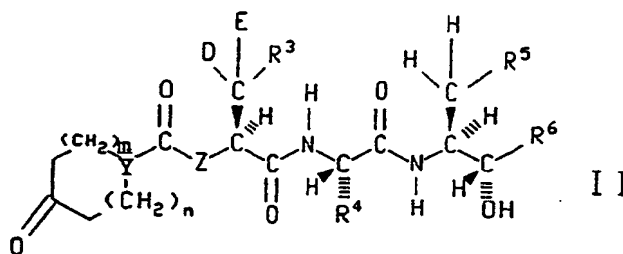
wherein R¹ and R² are independently selected from hydrogen, C₁ to C₈ alkyl, di(C₁ to C₃ alkyl)amino-C₂ to C₄ alkyl and nitrogen protecting groups or R¹ and R² taken together with the nitrogen to which they are attached form a ring which is morpholine, 4-methylpiperazine, pyrrolidine, or piperidine; I is 0, 1, 2 or 3; Y is N or CH; Z is NH, O or CH₂; R³ is phenyl, p-methoxyphenyl, benzyl, 1-naphthyl, cyclohexyl, 2-thienyl or 3-thienyl; and R¹⁰ is hydrogen, C₁ to C₃ alkyl or benzyl.

15. A compound of the formula



wherein Y is N or CH; Z is NH, O or CH₂; R³ is phenyl, p-methoxyphenyl, benzyl, 1-naphthyl, cyclohexyl, 2-thienyl or 3-thienyl; and R¹⁰ is hydrogen, C₁ to C₃ alkyl or benzyl.

16. A compound of the formula



wherein m and n are independently 0 or 1; Y is CH or N; Z is CH₂, NH, O or NCH₃; D and E are independently selected from hydrogen and C₁ to C₃ alkyl or D and E taken together with the carbon to which they are attached form a cyclopropyl, cyclobutyl or cyclopentyl ring; R³ is phenyl, cyclohexyl, 1-naphthyl, 2-thienyl, 3-thienyl, benzyl, or p-methoxybenzyl; R⁴ is C₁ to C₃ alkylthiomethyl, 4-imidazolylmethyl, C₁ to C₅ alkenylmethyl, C₁ to C₃ alkoxy-methyl or C₂ to C₄ alkyl; R⁵ is cyclohexyl; R⁶ is COO-C₁ to C₈ alkyl or CONR¹⁶R¹⁷ wherein R¹⁶ and R¹⁷ are independently selected from hydrogen and C₁ to C₅ alkyl, with the proviso that when Y is N and Z is NH or NHCH₃, then R⁴ is C₁ to C₅ alkenylmethyl, and the pharmaceutically acceptable salts thereof.

(19)



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C07D 211/46, C07D 277/28,
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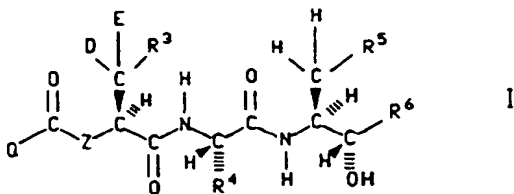
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(54) **Orally active renin inhibitors.**

(57) This invention relates to compounds of the formula



wherein Q, Z, D, E, R³, R⁴, R⁵ and R⁶ are defined as below, and the pharmaceutically acceptable salts thereof are disclosed. The compounds are useful as antihypertensive agents.

EP 0 438 233 A3



European Patent
Office

EUROPEAN SEARCH REPORT

Application Number

EP 91 30 0191

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
D,A	EP-A-0 266 950 (PFIZER INC.) * The whole document * ---	1,3,4, 11-14	C 07 K 5/02 A 61 K 37/64
D,A	EP-A-0 229 667 (ABBOTT LABORATORIES) * The whole document * ---	1,3,4, 11-14	C 07 D 211/56 C 07 D 205/04 C 07 D 339/02
D,A	EP-A-0 314 239 (MERCK & CO.) * The whole document * ---	1,3,4, 11-14	C 07 D 339/08 C 07 D 317/12 C 07 D 319/06
A	EP-A-0 337 334 (MERCK PATENT GmbH) * The whole document * -----	1,3,4, 11-14	C 07 D 211/46 C 07 D 277/28 C 07 D 277/64
The present search report has been drawn up for all claims			TECHNICAL FIELDS SEARCHED (Int. Cl.5)
			C 07 K C 07 D A 61 K
Place of search THE HAGUE		Date of completion of the search 11-03-1992	Examiner GROENENDIJK M.S.M.
CATEGORY OF CITED DOCUMENTS			
X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure F : intermediate document			
I : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document			

EPO FORM 1503 (03.82) (P0401)



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CLAIMS INCURRING FEES

The present European patent application comprised at the time of filing more than ten claims.

- ☐ All claims fees have been paid within the prescribed time limit. The present European search report has been drawn up for all claims.
- ☐ Only part of the claims fees have been paid within the prescribed time limit. The present European search report has been drawn up for the first ten claims and for those claims for which claims fees have been paid,
namely claims:
- ☐ No claims fees have been paid within the prescribed time limit. The present European search report has been drawn up for the first ten claims.

LACK OF UNITY OF INVENTION

The Search Division considers that the present European patent application does not comply with the requirement of unity of invention and relates to several inventions or groups of inventions,
namely:

see sheet -B-

- ☐ All further search fees have been paid within the fixed time limit. The present European search report has been drawn up for all claims.
- ☐ Only part of the further search fees have been paid within the fixed time limit. The present European search report has been drawn up for those parts of the European patent application which relate to the inventions in respect of which search fees have been paid,
namely claims:
- ☒ None of the further search fees has been paid within the fixed time limit. The present European search report has been drawn up for those parts of the European patent application which relate to the invention first mentioned in the claims,
namely claims: point 1.



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EP 91 30 0191 -B-

LACK OF UNITY OF INVENTION

The Search Division considers that the present European patent application does not comply with the requirement of unity of invention and relates to several inventions or groups of inventions, namely:

1. Claims 1,3,4,11-14(all partially):
Compounds of the formula I wherein Q is the first defined substituent (ketal or thioketal) and compositions containing them
2. Claims 2,5-10,15-18 (complete), 1,3,4,11,14 (all partially)
Compounds according to these claims as far as not covered by the first subject

Claim 1 of the present application relates to compounds having renin inhibiting activity, which are characterized by amino group(s) containing (hetero) cyclic residues at the N-terminal of known polypeptide structures (see EP 0 266 950 and EP 0 229 667).

At the date of filing of the present application substituents of the fore-mentioned character were already used to improve the properties of renin inhibiting compounds with similar structures (see especially EP 0 337 334, EP 0 314 239 and EP 0 229 667).

Although the application is lacking any information about the effect of these modifications (e.g. I.C. and/or stability to enzymatic degradation) it can be assumed that they bring about the same effect as those described in the state of the art.

For this reason the compounds of claim 1 are lacking a novel single general inventive concept common to all of them and therefore the requirements set forth in Art. 82 EPC are not fulfilled.

As the I.S.A. is bound to the content of Rule 46(1)EPC a partial search report has been drawn up for the subject first mentioned in the claims.



European Patent
Office

EP 91 30 0191 -B- -2-

LACK OF UNITY OF INVENTION

The Search Division considers that the present European patent application does not comply with the requirement of unity of invention and relates to several inventions or groups of inventions, namely:

The second subject still contains several distinct subjects. A search for this subject will therefore inevitably lead to a further non-unity objection. Therefore the applicants are invited to specify which embodiments of the present application they want to have searched and to pay a further fee for each subject.

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